CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 21936
Drug Name:	Spiriva Respimat (Tiotropium Bromide)
Indication(s):	Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), and for reducing COPD exacerbations
Applicant:	Boehringer Ingelheim
Date(s):	Receipt date: March 24, 2014
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Keywords: NDA, clinical studies

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

Spiriva HandiHaler (tiotropium bromide inhalation powder) was approved on January 30, 2004 for the long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. Boehringer Ingelheim (BI) proposes a newly developed pocket sized, multi-dose, soft mist inhaler for tiotropium inhalation solutions, referred to as Spiriva Respimat. The application was originally submitted on November 16, 2007 but received a Complete Response on September 16, 2008, citing two deficiencies, safety concerns of death and stroke, and lack of replicated evidence to support a claim for reducing COPD exacerbations. These deficiencies were addressed in the current submission. This review focuses on the efficacy of Spiriva Respimat for reducing COPD exacerbations.

Based on the results of study 205.372 (referred to as 372) and the evidence from the initial NDA review, there was replicated evidence to support a claim of reducing COPD exacerbations. In study 372 the first primary endpoint, change from baseline in trough FEV_1 at 48 weeks of treatment, demonstrated statistically significant effects for Spiriva Respimat over placebo. The pre-defined second primary efficacy endpoint, time to first COPD exacerbation, also showed a statistically significant improvement for Spiriva Respimat over placebo. There was a 31% reduction in the risk of time to first COPD exacerbation in a year for patients in the Spiriva Respimat group compared to those in the placebo group. Even though there were no adjustments for multiplicity, this evidence was supported by the analysis of secondary endpoints such as time to first hospitalization for COPD exacerbation, number of COPD exacerbations per patient, number of hospitalizations due to COPD exacerbations per patient, number of patients with at least one COPD exacerbation, and number of patients with at least one hospitalization due to COPD exacerbation. Further evidence to support the claim was demonstrated in study 205.452 (referred to as TIOSPIR) which was conducted mainly to address the safety concerns regarding death and stroke. In this study, the primary efficacy endpoint, time to first COPD exacerbation showed no significant differences between either of the Spiriva Respimat groups compared to Spiriva HandiHaler nor was any differences shown between Spiriva Respimat 2.5 mcg compare vs. Spiriva Respimat 5 mcg.

The Pulmonary-Allergy Drugs Advisory Committee convened on August 14, 2014 to discuss the efficacy data including data to support the claim for reduction of COPD exacerbations, but the focus was mainly on safety findings from the clinical development program and the results of a large safety study comparing tiotropium bromide inhalation spray and tiotropium bromide inhalation powder. The committee voted 13 to 0 in favor of the efficacy data providing substantial evidence of a clinically meaningful benefit for Spiriva Respimat 5 mcg for the long-term, once-daily maintenance treatment of bronchospasm associated with COPD and for reducing COPD exacerbations when compared to placebo. The committee voted 9 to 4 in favor of the safety data adequately addressing the safety concerns with Spiriva Respimat 5 mcg, including the mortality imbalance noted in the 48 week phase 3 studies. The committee voted 10 to 3 in favor of recommending the approval of Spiriva Respimat 5 mcg for the long term once-daily maintenance treatment of bronchospasm associated with COPD and for reducing COPD exacerbations.

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Boehringer Ingelheim (BI) proposes tiotropium inhalation solutions, an approved drug, delivered in a newly developed pocket sized, multi-dose Respimat soft mist inhaler in patients with COPD. The sponsor is also requesting an indication for reduction of COPD exacerbations.

2.1.2 History of Drug Development

BI had several interactions with the Division of Pulmonary, Allergy, and Rheumatology Products regarding tiotropium (under IND 65,127). Pertinent parts of the statistical portion pertaining to efficacy of the communications and interactions for the tiotropium program are summarized herein.

BI submitted an application (NDA 21-936) on November 16, 2007. All studies submitted are shown in Table 1. The application included two replicate one-year studies, 205.254 (referred to as 254) and 205.255 (referred to as 255), in patients with COPD. The 5 mcg Spiriva Respimat and 10 mcg Spiriva Respimat groups each had statistically significantly better average outcomes in terms of the four co-primary efficacy endpoints (trough FEV_1 at the end of the 48-week treatment period, St. Georges's Respiratory Questionnaire (SGRQ) total score at the end of the 48-week treatment period, Mahler Transition Dyspnoea Index (TDI) focal score at the end of the 48-week treatment period, and number of COPD exacerbations in one year) than the placebo group. Note that the differences between both Spiriva Respimat groups and placebo were statistically significantly in favor of the Spiriva Respimat groups for trough FEV_1. However, the difference in the number of COPD exacerbations was statistically significantly in favor of each Spiriva Respimat group over placebo in study 255 but not in study 254. Thus, the COPD claim had not been replicated. The submission also included two 12 week studies, 205.251 (referred as 251) and 205.252 (referred as 252). In both of the 12-week studies in patients with COPD, the 5 mcg Spiriva Respimat and 10 mcg Spiriva Respimat groups each had statistically significantly better average trough FEV_1 at 12-weeks than the placebo groups. Refer to Dr. Ruthanna Davi's statistical review for specific details regarding the design, analysis plan, and efficacy results of studies 251, 252, 254 and 255, dated August 26, 2008.

Table 1. Summary of Spiriva Clinical Development Program

Study ID	Length of the Study	Treatment Arms*	Number of Patients	Study Population	Primary Efficacy Endpoint(s)
251	12 weeks	SR 5 mcg SR 10 mcg IB 36 mcg Placebo	88 93 89 91	COPD	Trough FEV_1
252	12 weeks	SR 5 mcg SR 10 mcg IB 36 mcg Placebo	92 87 89 90	COPD	Trough FEV_1
254	48 weeks	SR 5 mcg SR 10 mcg Placebo	332 332 319	COPD	Trough FEV_1, SGRQ, TDI, Number of COPD exacerbations
255	48 weeks	SR 5 mcg SR 10 mcg Placebo	338 335 334	COPD	Trough FEV_1, SGRQ, TDI, Number of COPD exacerbations

Source: Reviewer
* SR=Spiriva Respimat; IB=Ipratropium Bromide; SHH=Spiriva HandiHaler

The Division issued a Complete Response letter on September 16, 2008 in response to NDA 21-936. One of the comments provided by the Division that identified the deficiency that precluded approval of that application is shown below:

> Deficiency:
> The submitted data do not provide substantial evidence to support the proposed claim of reduction of COPD exacerbation. While the pre-specified combined analysis of the two 48-week clinical studies 205.254 and 205.255 show a decreased number of COPD exacerbations with Spiriva Respimat compared to placebo, replication of the finding is necessary to support a labeling claim. Results of the two individual 48-week studies are not sufficient for replication because only one of the two studies showed a statistically significant difference from placebo.
>
> Information Needed to Resolve the Deficiency:
> To support the proposed claim of reduction of COPD exacerbation, provide data from an adequate and well controlled clinical study that shows statistically significant reduction in COPD exacerbation with Spiriva Respimat compared to placebo.

On May 10, 2013 the Division responded to BI with written responses referring to the resubmission of NDA 21-936 for Spiriva Respimat. BI planned to provide information to support the proposed indication of the reduction of COPD exacerbation. The applicant stated that the primary support for the indication of reduction in COPD exacerbations would come from study 372, a placebo controlled study. The applicant anticipated that the TIOSPIR study would provide

additional support for the Spiriva Respimat exacerbation outcome. The Division responded by saying, pending review of trial data, your strategy is generally reasonable.

2.1.3 Specific Studies Reviewed

This review will focus on the results from study 372; however, the results from the TIOSPIR study will be used to support the exacerbation claim.

2.2 Data Sources

The resubmission of NDA 21-936 was submitted on March 24, 2014. The study reports including protocols, statistical analysis plan, and all referenced literature were submitted by the applicant to the Agency. The data and final study report for the electronic submission were archived under the network path location \\CDSESUB1\evsprod\NDA021936\003.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

In general, the electronic data submitted by the applicant were of sufficient quality to allow a thorough review of the data. I was able to reproduce the analyses of the primary and secondary efficacy endpoints for each clinical study submitted and were able to verify the randomization of the treatment assignments.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

A summary of the study design and endpoints for studies 372 and TIOPSIR are shown in Table 2. Each study is discussed separately in sections 3.2.1.1 and 3.2.1.2. Note the definition of a COPD exacerbation was the same for both studies and was defined as a complex of respiratory events/symptoms (increase or new onset) with a duration of 3 days or more requiring a change in treatment. A complex of respiratory events/symptoms was defined as at least 2 of the following:

- Shortness of breath/dyspnea/shallow, rapid breathing
- Sputum production (volume)
- Occurrence of purulent sputum
- Cough
- Wheezing
- Chest tightness

Exacerbations were categorized as mild (treated at home without seeing a healthcare provider), moderate (visit with healthcare provider, e.g. home visit, visit to an outpatient facility or an

emergency department but not requiring admission to hospital), or severe (hospitalizations; an emergency department stay >24 hours was considered a hospitalization).

Table 2. Summary of Study Design and Endpoints

Study ID	Length of the Study	Treatment Arms*	Number of Patients	Study Population	Primary Efficacy Endpoint(s)
372	1 year	SR 5 mcg Placebo	1989 2002	COPD	ΔFEV_1 trough baseline to week 48, time to 1st COPD exacerbation
TIOSPIR	Event Driven	SR 2.5 mcg SR 5 mcg SHH 18 mcg	5724 5705 5687	COPD	Time to 1st COPD exacerbation

Source: Reviewer
* SR = Spiriva Respimat; SHH= Spiriva HandiHaler

3.2.1.1 Study 372

Study 372 was a phase 3, randomized, double-blind, parallel-group, placebo-controlled, multi-center, multi-national 1-year study. The study was designed to evaluate the long term safety and efficacy of Spiriva Respimat 5 mcg (2 puffs of 2.5 mcg) administered once daily in the morning in patients with COPD. The baseline FEV_1 was defined as the pretreatment FEV_1 measurement at visit 2 in the morning prior to the first dose of randomization treatment. The study contained two primary endpoints, change from baseline in trough FEV_1 on day 337 and time to first COPD exacerbation. Secondary exacerbation endpoints were time to first hospitalization for COPD exacerbation, number of COPD exacerbations per patient, number of hospitalizations due to COPD exacerbations per patient, number of patients with at least one COPD exacerbation, and number of patients with at least one hospitalization due to COPD exacerbation.

3.2.1.2 TIOSPIR

TIOSPIR was a randomized, active-controlled, double-blind, double-dummy, parallel group, multi-center mortality study conducted mainly to address the safety concerns regarding death and stroke. This active-comparator study compared Spiriva Respimat to Spiriva HandiHaler, which is currently being marketed. Patients were randomized to receive either Spiriva Respimat 2.5 mcg or 5 mcg or Spiriva HandiHaler 18 mcg. All patients received placebo along with active treatment. TIOSPIR was an event-driven study that was designed to continue until 1,266 fatal events were reported. The first primary endpoint was time to all-cause mortality (a safety endpoint). The second primary endpoint was time to first COPD exacerbation (an efficacy endpoint). The secondary efficacy endpoints were number of COPD exacerbations, time to first COPD exacerbation associated with hospitalization, number of COPD exacerbations associated with hospitalization, and time to first moderate to severe COPD exacerbation. The secondary safety endpoints were time to first occurrence of major adverse cardiovascular event (MACE) and time to death from MACE.

3.2.2 Statistical Methodologies

3.2.2.1 Study 372

The randomized set (RAN) included all patients, whether they were treated or not. All efficacy analyses were performed using the full analysis set (FAS), which was defined as all randomized patients that were given and documented to have taken at least one dose of double-blind randomized treatment. Patients randomized at sites 1008 (8 patients), 3314 (17 patients), and 91009 (74 patients) were deemed to have questionable data and were excluded from the FAS. The protocol specified that in study 372 the first primary endpoint, change from baseline in trough FEV_1, was analyzed using an analysis of covariance (ANCOVA) model with fixed effects of center, long-acting beta adrenergics (LABA) use, and treatment and the baseline trough FEV_1 as a covariate. An analysis utilizing the RAN set was also conducted.

The last observation carried forward (LOCF) method was used for missing data for the first primary endpoint, change from baseline in trough FEV_1. If an assessment was missing then the last non-missing post-baseline value was imputed. However, those patients that discontinued early due to unexpected worsening of COPD, the least favorable (worst) prior observation was carried forward (WOCF). Baseline data was not be carried forward. LOCF is a single imputation method which assumes data is missing at random (MAR) or missing completely at random, which in the current clinical setting may not be a valid assumption. The above methods were consistent with the previous review of studies 254 and 255 where the efficacy of Spiriva Respimat for treatment of bronchodilation was established. In Dr. Davi's review these methods were found to be robust against concerns regarding missing data. Based on this information and that the missing data were similar between studies (note study 372 had less missing data than studies 254 and 255), I found this approach acceptable.

For the two primary efficacy endpoints in study 372, change from baseline in trough FEV_1 and time to first COPD exacerbation, a stepwise manner was used to protect the overall type I error. If superiority of Spiriva Respimat over placebo was established for change from baseline in trough FEV_1, then the treatment groups were compared for the time to first COPD exacerbation. As per protocol, the second primary endpoint, time to first COPD exacerbation during the randomized treatment period, was analyzed using a Cox's proportional hazards model that included terms for center, LABA use and treatment. Only COPD exacerbations with an onset during the randomized treatment period were included; exacerbations starting on the day after the last dose of randomized treatment were considered as 'on-treatment' and included in the analysis.

Various secondary endpoints related to exacerbations were included to support the second primary endpoint, time to first COPD exacerbation. Time to first hospitalization for COPD exacerbation was analyzed using a Cox's proportional hazards model that included terms for center, LABA use, and treatment. Only COPD exacerbations with an onset during the randomized treatment period were included; exacerbations starting on the day after the last dose of randomized treatment was taken were considered as 'on-treatment' and therefore included in the analysis. The number of COPD exacerbations and the number of hospitalizations related to

COPD exacerbations were analyzed using a generalized linear model regression analysis assuming a Poisson distribution correcting for overdispersion. The number of patients with at least one COPD exacerbation and the number of patients with at least one hospitalization due to COPD were analyzed using a logistic regression analysis with center, LABA use treatment exposure and treatment included in the model. There were no adjustments for multiplicity with respect to the secondary efficacy variables.

Subgroup analyses were conducted by LABA use on the primary efficacy endpoints as well as number of COPD exacerbations and proportion of patients experiencing at least one COPD exacerbation.

3.2.2.2 TIOSPIR

The analysis for the primary efficacy endpoint, time to first COPD exacerbation, was analyzed using a Cox's proportional hazards regression model with no covariate adjustment. The primary comparison of interest was the superiority of Spiriva Respimat 5 mcg over Spiriva HandiHaler 18 mcg. The applicant also compared the treatment Spiriva Respimat 2.5 mcg vs. Spiriva HandiHaler 18 mcg and Spiriva Respimat 2.5 mcg vs. Spiriva Respimat 5 mcg.

The analyses in the TIOSPIR study were conducted in the treated set (TS) which was defined as all randomized patients who received at least one dose of study medication excluding randomized patients enrolled at sites 1280 or 49157 (19 patients between the two sites).

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Study 372

The summary of the patient disposition for the treated set (TS) in study 372 is given in Table 3. The treated set was defined as all patients who were dispensed and documented to have taken at least 1 dose of double blind randomized treatment and not been randomized to site 91009 with questionable treatment assignment/administration. Approximately 17% of the patients discontinued study medication. The primary reason for discontinuation in both groups was adverse advents (AE) with 7% in the tiotropium group and 8% in the placebo group. More patients discontinued due to lack of efficacy in the placebo group with 3% compared to the Spiriva Respimat group with 1%. Protocol violations accounted for about 2% overall for the discontinuations.

Table 3. Summary of Patient Disposition in Study 372

	Spiriva Respimat n (%)	Placebo n (%)
Randomized	1989	2002
Completed	1671 (84)	1929 (81)
TS	1952 (98)	1965 (98)
FAS	1939 (98)	1953 (98)
Discontinued	318 (16)	373 (19)
Adverse Event	143 (7)	156 (8)
Worsening of disease under study	46 (2)	77 (4)
Worsening of other pre-existing disease	14 (1)	7 (0.3)
Other	83 (4)	72 (4)
Lack of Efficacy	28 (1)	67 (3)
Non-compliant with protocol	47 (2)	35 (2)
Lost to Follow-up	22 (1)	28 (1)
Consent withdrawn	20 (1)	35 (2)
Other	58 (3)	52 (3)

Source: Clinical Trial Report-Protocol Number 205.372 Table 10.1:1, page 76

The patients' mean age was about 65 years. Most of the patients were White (69%) and male (78%) in this study. These factors were generally well-balanced across the treatment groups. The summary of the demographics is given in Table 4.

Table 4. Summary Demographics Characteristics in Study 372 - (Treated Set)

	Spiriva Respimat N=1952	Placebo N=1965
Age (years)		
Mean (SD)	65 (9)	65 (9)
Sex n (%)		
Female	428 (22)	452 (23)
Male	1524 (78)	1513 (77)
Race n (%)		
White	1343 (69)	1346 (68)
Black	29 (1)	38 (2)
Asian	580 (30)	581 (30)
Height (cm)		
Mean (SD)	168 (7)	168 (9)
Weight (kg)		
Mean (SD)	71 (18)	71 (18)
Smoking Status, n (%)		
Never smoked	1 (<1)	0
Ex-smoker	1254 (64)	1260 (64)
Current smoker	697 (36)	705 (36)
Smoking History (pack years)		
Mean (SD)	46 (26)	45 (27)
Duration of COPD (years)		
Mean (SD)	8 (7)	8 (7)

Source: Clinical Trial Report-Protocol Number 205.372 Table 11.2:1, page 80

3.2.3.2 TIOSPIR

The summary of the patient disposition in the TIOSPIR study is given in Table 5. Approximately 23% of the patients withdrew from the study medication. The primary reason for discontinuation in both groups was AEs with 11% in each group. Patient refusal to continue taking study drug was about 6% overall.

Table 5. Summary of Patient Disposition in TIOSPIR (Treated Set)

	SR* 2.5 N (%)	SR* 5 N (%)	SHH* 18 N (%)
Randomized	5741	5729	5713
Treated	5724 (100)	5705 (100)	5687 (100)
Completed	4400 (77)	4399 (77)	4400 (77)
Discontinued	1324 (23)	1306 (23)	1787 (23)
Adverse Event	602 (11)	606 (11)	635 (11)
Worsening of disease under study	170 (3)	171 (3)	185 (3)
Worsening of other disease	47 (<1)	45 (<1)	58 (1)
Other AE	385 (7)	390 (7)	392 (7)
Lack of efficacy	65 (1)	60 (1)	59 (1)
Non-compliant with protocol	64 (1)	66 (1)	41 (<1)
Lost to follow-up	52 (1)	63 (1)	55 (1)
Patient refused to continue taking study medication	331 (5)	335 (6)	319 (6)
Other	210 (4)	176 (3)	178 (3)

Source: Clinical Trial Report-Protocol Number 205.452 Table 10.1:1, page 84
* SR = Spiriva Respimat; SHH: Spiriva HandiHaler

The demographics and baseline characteristics in the TIOSPIR study is summarized in Table 6 for the TS population. The patients' mean age was about 65 years. Most of the patients were White (82%) and male (71%) in this study. These factors were generally well-balanced across the treatment groups.

Table 6. Summary of Demographics Characteristics in TIOSPIR - (Treated Set)

	SR* 2.5 N (%)	SR* 5 N (%)	SHH* 18 N (%)
Number of patients, N (%)	5724 (100)	5705 (100)	5687 (100)
Gender, N (%)			
Male	4068 (71)	4134 (73)	4035 (71)
Female	1656 (29)	1571 (27)	1652 (29)
Race, N (%)			
White	4683 (82)	4650 (81)	4630 (81)
Black	77 (1)	94 (2)	85 (2)
Asian	810 (14)	802 (14)	816 (14)
Missing	154 (3)	159 (3)	156 (3)
Age (years)			
Mean (SD)	65 (9)	65 (9)	65 (9)
BMI (kg/m^2)			
Mean (SD)	26 (6)	26 (6)	26 (6)
Duration of COPD (years)			
Mean (SD)	7 (6)	7 (6)	7 (6)
Smoking History, N (%)			
Never smoked	1 (0)	1 (0)	1 (0)
Ex-smoker	3556 (62)	3496 (61)	3542 (62)
Currently smokes	2167 (38)	2208 (39)	2144 (38)

Source: Clinical Trial Report-Protocol Number 205.452 Table 11.2.1:1, page 91-92
* SR = Spiriva Respimat; SHH: Spiriva HandiHaler

3.2.4 Results and Conclusions

3.2.4.1 Study 372

The results from the primary efficacy analysis will be shown in the order of the hierarchical testing procedure. Change from baseline in trough FEV_1 was tested first, if significant, time to first COPD exacerbation was tested.

The pre-specified primary efficacy analysis for the first primary endpoint, change from baseline in trough FEV_1, is shown in Table 7. The Spiriva Respimat treatment group showed a statistically significant improvement in the mean change from baseline in trough FEV_1 compared to the placebo group, 0.12 L versus 0.02 L, respectively. Note 74 patients were excluded from the FAS population due to questionable drug receipt and dispensing logs from one of the sites. This analysis also excluded an additional 25 patients, 17 patients who were found to be participating in another study and 8 patients that had questionable drug accountability data. The results using the RAN set concurs with the results from the primary analysis. To examine the effects of missing data, an average FEV_1 baseline was assigned to the missing data. The results were consistent with the sponsor's results.

Table 7. Results from Analysis of First Primary Endpoint, Mean Change from Baseline in Trough FEV_1 (L) in Study 372 (FAS Population)

Mean Trough FEV_1 (L)	Spiriva Respimat N=1889*	Placebo N=1870*
Baseline	1.11	1.11
Day 337	1.23	1.13
Change from baseline	0.12	0.02
Difference from placebo	0.10	
95% CI	0.09, 0.12	
p-value	<0.0001	

*: Number of observations used in the analysis
Source: Adapted from Clinical Trial Report-Protocol Number 205.372 Table 11.4.1.1.1:1, page 86

Since the comparison for the first primary endpoint, change from baseline in trough FEV_1 was statistically significant in favor of Spiriva Respimat and according to the pre-specified multiplicity plan; inferential statistical analysis may proceed to the second primary endpoint, time to first COPD exacerbation.

The results for time to first COPD exacerbation are shown in Table 8. This analysis also included exacerbations that started on the day after the last intake of study medication. There was a 31% reduction in the risk of time to first COPD exacerbation in a year for patients in the Spiriva Respimat group compared to those in the placebo group. This was based on the estimated hazard ratio, using the Cox model, of 0.69 [95% CI: (0.63, 0.77)] between Spiriva Respimat and placebo. This analysis excluded patients enrolled at sites 1008, 3314 and 91009.

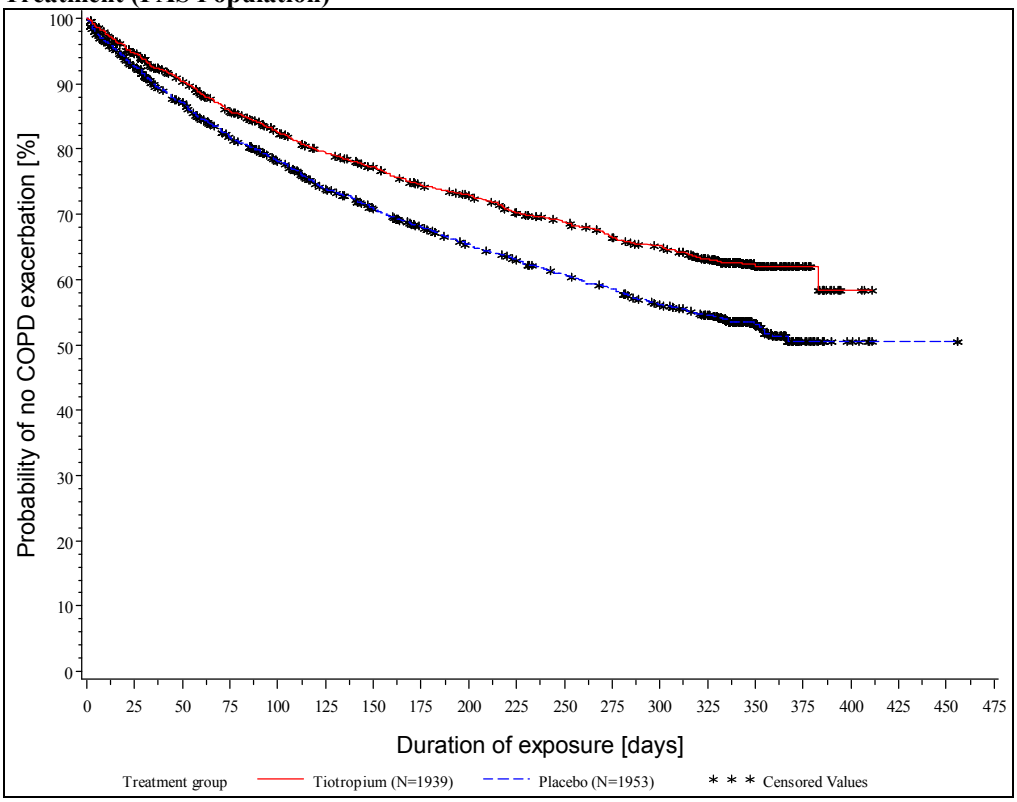
Table 8. Results from Analysis of the Second Primary Endpoint, Time to First COPD Exacerbation in Study 372 (FAS Population)

	Spiriva Respimat N=1939	Placebo N=1953
Number of patients with at least one exacerbation, n (%)	685 (35)	842 (43)
Number censored patients, n (%)	1254 (65)	1111 (57)
Hazard Ratio vs. placebo	0.69	
95% CI	0.63, 0.77	
p-value	<0.0001	

Source: Adapted from Clinical Trial Report-Protocol Number 205.372 Table 11.4.1.1.2:1, page 88

The Kaplan-Meier plot of time to first COPD exacerbation is shown in Figure 1.

Figure 1. Kaplan-Meier Estimates of the Probability of No COPD Exacerbations during Randomized Treatment (FAS Population)



Source: Clinical Trial Report-Protocol Number 205.372 Figure 15.2.2.1:1, page 308
Note: Tiotropium refers to Spiriva Respimat

Since the results shown in Table 8 and Figure 1 excluded subjects enrolled at sites 1008, 3314 and 91009, I conducted an analysis where the data from these sites were included. The results were consistent with the primary analysis, results not shown.

I examined several additional secondary endpoints, time to first hospitalization for COPD exacerbation, number of COPD exacerbations per patient, number of hospitalizations due to COPD exacerbations per patient, number of patients with at least one COPD exacerbation, and number of patients with at least one hospitalization due to a COPD exacerbation to support the analyses of time to first COPD exacerbation. There were no pre-specified multiplicity corrections in place for any of these secondary endpoints and they were conducted using the FAS dataset. The results for time to first hospitalization for due to a COPD exacerbation are shown in Table 9. There was evidence that Spiriva Respimat reduced the risk of COPD exacerbation leading to hospitalization by 27% (a quarter of an event in one year) compared with placebo.

Table 9. Results for Analysis of Time to First Hospitalization Due to COPD Exacerbations in Study 372 (FAS Population)

	Spiriva Respimat N=1939		Placebo N=1953
Number of patients with at least one exacerbation, n (%)	161 (8)		198 (10)
Number censored patients, n (%)	1778 (92)		1755 (90)
Hazard Ratio vs. placebo		0.73	
95% CI		0.59, 0.90	
p-value		0.0034	

Source: Clinical Trial Report-Protocol Number 205.372 Table 11.4.1.2.2:1, page 91
The Cox proportional hazard ratio was adjusted for pooled center and LABA use

Table 10 shows the results for number of COPD exacerbations and number of hospitalizations due to COPD exacerbations. Both analyses were statistically significantly different in favor of Spiriva Respimat.

Table 10. Result from Analyses of Number of COPD exacerbations and number of Hospitalizations Due to COPD Exacerbations in Study 372 (FAS Population)

	Spiriva Respimat N=1939		Placebo N=1953
Patient years at risk	1645		1608
Number of COPD Exacerbation	1168		1434
Mean Rate (95% CI)	0.69 (0.64, 0.74)		0.87 (0.82, 0.93)
Relative rate vs. placebo		0.79	
95% CI		0.72, 0.87	
p-value		<0.0001	
Number of Hospitalizations Related to COPD Exacerbations	210		253
Mean Rate (95% CI)	0.12 (0.11, 0.14)		0.15 (0.14, 0.17)
Relative rate vs. placebo		0.81	
95% CI		0.70, 0.93	
p-value		0.0036	

Source: Clinical Trial Report-Protocol Number 205.372 Table 11.4.1.2.2:2, page 94
From regression model assuming a Poisson distribution correcting for overdispersion and adjusting for time at risk and LABA use

Table 11 shows the results for number of patients with at least one COPD exacerbation and at least one hospitalization due to COPD exacerbation. Patients taking Spiriva Respimat are associated with lower odds of having at least one exacerbation in a year than those patients on placebo. There was not a significant difference between patients on Spiriva Respimat and patients on placebo for number of patients with at least one hospitalization due to COPD

exacerbation. However, there was a numerical trend in favor of Spiriva Respimat for number of patients with at least one hospitalization due to COPD.

Table 11. Summary of Number of Patients with at Least One COPD Exacerbation and Hospitalizations Due to COPD Exacerbation in Study 372 (FAS Population)

	Spiriva Respimat N=1939		Placebo N=1953
Patient years at risk	1645		1608
Number of patients with at least one COPD Exacerbation, n (%)	685 (35)		842 (43)
Odds ratio vs. placebo		0.70	
95% CI		0.62, 0.80	
p-value		<0.0001	
Number of Patients with at least one Hospitalizations Related to COPD Exacerbations, n (%)	161 (8)		198 (10)
Odds ration vs. placebo		0.82	
95% CI		0.66, 1.02	
p-value		0.0728	

Source: Clinical Trial Report-Protocol Number 205.372 Table 11.4.1.2.2:3, page 96
A logistic regression analysis, with LABA use, treatment exposure and treatment included in the model

The results from these secondary analyses support the second primary endpoint, time to first COPD exacerbation.

3.2.4.2 TIOSPIR

The results for the primary efficacy analysis, time to first COPD exacerbation, are shown in Table 12.

Table 12. Results from the Analysis of Time to First COPD Exacerbation in TIOSPIR (Treated Set)

	SR* 2.5 N (%)	SR* 5 N (%)	SHH* 18 N (%)
Number of patients	5724 (100)	5705 (100)	5687 (100)
Patients with COPD exacerbations	2827 (49)	2733 (48)	2782 (49)
Comparison vs. SHH 18			
Hazard ratio	1.02	0.98	
95% CI	0.96, 1.07	0.93, 1.03	
p-value	0.5593	0.4194	
Comparison vs. SHH 5			
Hazard ratio	1.04		
95% CI	0.99, 1.09		
p-value	0.1639		

Source: Clinical Trial Report-Protocol Number 205.452 Table 11.4.1.1.2:1, page 105
* SR: Spiriva Respimat; SHH: Spiriva HandiHaler

There were no statistically significantly differences between either of the Spiriva Respimat groups when compared to Spiriva HandiHaler. Thus, there was not sufficient evidence to conclude that Spiriva Respimat was different from Spiriva HandiHaler 18 mcg with regards to time to first COPD exacerbation. Even though these results cannot be used to conclude the Spiriva Respimat is non-inferior to Spiriva HandiHaler they could be considered as supportive information.

3.3 Evaluation of Safety

Safety evaluations for this submission will be evaluated by the Medical Reviewer, Robert Lim, M.D and Statistical Reviewer Bo Li, Ph.D. Please refer to their reviews for more details regarding the safety findings.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses for age, gender, and race were reviewed previously in studies 254 and 255 (no differences were noted); hence this submission did not consider these subgroups. This submission looked at differences in efficacy due to LABA use where LABA use was defined as a patient using a LABA before or on the date randomized that continues for one or more days after randomization. Tables 13 and 14 summarize the efficacy results by LABA use (yes/no) for the primary endpoints, change from baseline in trough FEV_1 and time to first COPD exacerbation, respectively in study 372. There were statistically significant differences in favor of Spiriva Respimat at day 337 regardless of LABA use for both endpoints.

Table 13. Summary First Primary Endpoint by LABA Use in Study 372 (FAS population)

	Spiriva Respimat		Placebo
LABA use: Yes	N=1027		N=982
Mean Baseline	1.11		1.11
Day 337, mean	1.22		1.11
Mean Change from baseline	0.11		0.001
Mean Treatment Δ to placebo		0.10	
95% CI		0.08, 0.13	
p-value		<0.0001	
LABA use: No	N=862		N=888
Mean Baseline	1.11		1.11
Day 337, mean	1.24		1.14
Mean Change from baseline	0.13		0.03
Mean Treatment Δ to placebo		0.10	
95% CI		0.07, 0.13	
p-value		<0.0001	

Source: Clinical Trial Report-Protocol Number 205.372 Table 15.2.1:4, page 304-305

Table 14. Summary Second Primary Endpoint by LABA Use in Study 372 (FAS Population)

	Tiotropium		Placebo
LABA use: Yes	N=1051		N=1025
Number of patients with at least one exacerbation, n (%)	436 (42)		485 (47)
Number censored patients, n (%)	615 (58)		540 (53)
Hazard Ratio vs. placebo		0.76	
95% CI		0.66, 0.87	
p-value		0.0001	
LABA use: No	N=888		N=928
Number of patients with at least one exacerbation, n (%)	249 (28)		357 (39)
Number censored patients, n (%)	639 (72)		571 (61)
Hazard Ratio vs. placebo		0.63	
95% CI		0.53, 0.76	
p-value		<0.0001	

Source: Clinical Trial Report-Protocol Number 205.372 Table 15.2.2.1:3, page 311-312

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

During the course of this review two information requests were sent to the applicant. The first was for study 372, where the full dataset for time to first COPD exacerbation was requested. The second information request was for the TIOSPIR study, requesting the exacerbation efficacy datasets and variables used in the efficacy analysis. The applicant submitted the required information. Missing data for trough FEV_1 were, according to the protocol, imputed with a combination of WOCF and LOCF. To examine the impact of this approach, I assigned an average baseline to all missing data; the results were consistent with the primary efficacy analysis. No further statistical issue were identified.

5.2 Conclusions and Recommendations

In study 372, the first primary endpoint, change from baseline in trough FEV_1 at 48 weeks demonstrated a statistically significant treatment effect in favor of Spiriva Respimat over placebo. The second primary endpoint, time to first COPD exacerbation, also showed a statistically significant improvement for Spiriva Respimat over placebo. For the proposed dose of Spiriva Respimat, there was a 31% reduction in the risk of time to first COPD exacerbation in a year for patients in the Spiriva Respimat group compared to those in the placebo group. The analyses of the secondary endpoints, time to first hospitalization for COPD exacerbations, numbers of COPD exacerbations, number of hospitalizations related to COPD exacerbations, and number of patients with at least one COPD exacerbation support the exacerbation claim.

In the TIOSPIR study, the primary efficacy endpoint, time to first COPD exacerbation showed no statistically significant differences between either of the Spiriva Respimat groups compared to Spiriva HandiHaler nor was there any statistically significant difference between the Spiriva Respimat 2.5 mcg compared to Spiriva Respimat 5 mcg.

Based on the results from study 372, the supportive evidence from the TIOSPIR study, and studies previously reviewed in the initial NDA, the efficacy of Spiriva Respimat 5 mcg for maintenance treatment of bronchospasm associated with COPD and reduction of COPD exacerbations was demonstrated.

5.3 Comment on the Proposed Label

The focus of the labeling review is on Sections 6 and 14. Edits to the label are pending. Based on the preliminary review of the label, we have the following general comments for consideration:

Section 6:

- Include information about the TIOSPIR study

Section 14:

- Add the dose-ranging studies
- Lung Function
    - Remove TIOSPIR study
    - Remove some of the figures
    - Remove results of the serial FEV_1 data
    - Add results of the primary endpoint, trough FEV_1, from the studies reviewed
- Exacerbations
    - Remove tables with secondary endpoints
    - Remove figure
    - Remove TIOSPIR study

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/s/

KIYA HAMILTON
08/29/2014

DAVID M PETULLO
08/29/2014

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 21-936
Drug Name:	Tiotropium Inhalation Solution delivered by the Respimat Inhaler
Indication(s):	Treatment of COPD
Applicant:	Boehringer Ingelheim
Date(s):	Submitted: March 24, 2014 PDUFA Goal Date: September 24, 2014
Review Priority:	Resubmission
Biometrics Division:	Division of Biometrics VII
Statistical Reviewer:	Bo Li, Ph.D., Statistical Reviewer
Concurring Reviewers:	Mat Soukup, Ph.D., Team Leader Aloka Chakravarty, Ph.D., Division Director
Medical Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Clinical Team:	Robert Lim, M.D., Medical Officer Anthony Durmowicz, M.D., Lead Medical Officer Sally Seymour, M.D., Division Director for Safety
Project Manager:	Jessica Lee (DPARP)

Keywords: clinical studies, COPD, safety, mortality

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. EXECUTIVE SUMMARY

The proposed indication for Spiriva Respimat is for the long-term, once-daily maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema in adults. The proposed dose with the Respimat device is two inhalations once daily for a total dose of 5 mcg (2.5 mcg/ actuation) tiotropioum. Tiotropium is a specific antagonist at muscarinic acetylcholine receptors called anticholinergic.

The initial NDA for Spiriva Respimat was submitted on November 16, 2007. The Agency issued a Complete Response Letter on September 16, 2008, which concluded that this application could not be approved in its present form. One safety deficiency was that increased frequencies of death were observed in subjects treated with Spiriva Respimat compared to placebo in the two 48-week exacerbation studies (Studies 205.254 and 205.255) submitted with the initial application.

The applicant resubmitted the Spiriva Respimat NDA (NDA 21-936) on March 24, 2014. They seek to address the question on fatal events primarily based on the information derived from the new long-term, large-scale clinical study 205.452 (TIOSPIR). TIOSPIR was designed and powered to evaluate the risk of all-cause mortality associated with the use of the Spiriva Respimat inhalation device, compared to the Spiriva HandiHaler device which has been approved by the Agency and marketed since 2004. TIOSPIR was powered to rule out a relative excess mortality risk of 25% for Spiriva Respimat (5 mcg daily and 2.5 mcg daily) vs. Spiriva HandiHaler (18 mcg daily). It provides a total of 34,085 patient years of treatment exposure to Spiriva which includes 11,343 patient years of exposure to the proposed dose of Respimat 5 mcg. Of the 17,135 randomized subjects, 99.7% had vital status confirmed until the event-driven end of the trial, when a total of 1302 deaths were observed. Among the 1302 deaths, 439 were reported (incidence rate of 3.4 events per 100 person years) on the HandiHaler 18mcg treatment arm, 440 were reported (incidence rate of 3.3 events per 100 person years) on the Respimat 2.5 mcg arm and 423 were reported (incidence rate of 3.2 events per 100 person years) on the Respimat 5 mcg arm.

The pre-specified primary analysis was based upon a Cox proportional hazards model utilizing an “on-study” censoring scheme for the primary endpoint of time to death from any cause. The results of the primary analysis shows no evidence of excess risk of all-cause mortality associated with use of the Respimat device for either dose (2.5mcg and 5mcg) compared to the HandiHaler device and successfully ruled out the pre-defined risk margin of 1.25 (Table 1). The estimated hazard ratio of Respimat 5 mcg vs. HandiHaler is 0.96 with a 95% CI of (0.84, 1.09). Utilizing alternate events and events ascertainment strategies, results of sensitivity analyses are consistent with that of the primary analysis of mortality.

Table 1: Primary Analysis Result of Mortality in TIOSPIR

	SHH 18mcg (N = 5694)	SR 2.5mcg (N = 5730)	SR 5mcg (N = 5711)
On-study Analysis of Death			
Number (%) of **Death**	439 (7.7)	440 (7.7)	423 (7.4)
Incidence Rate per 100 PY	3.4	3.3	3.2
HR (95% CI) , vs. SHH 18mcg		**1.00 (0.87, 1.14)**	**0.96 (0.84, 1.09)**

Source: Created by reviewer.

In the NDA resubmission additional supplemental data on mortality was submitted in a so-called placebo-controlled vital status database (VSD) which integrates the vital status information collected from four randomized, double-blind, placebo-controlled Respimat clinical trials with a parallel group design of at least 24 weeks duration. These include three Phase 3 exacerbation trials (Studies 205.254, 205.255 from the original NDA and a more recent trial, Study 205.372) and one Phase 3 bronchodilation trial (Study 1205.14). Refer to Section 2 for a description of the four trials.

In these efficacy trials of Spiriva Respimat, vital status information was followed and collected either retrospectively or prospectively for those subjects who discontinued their randomized treatment prematurely. At the end of the fixed duration of these four studies, vital status was confirmed for 98.5% of all treated subjects randomized to either the SR 5mcg group (2395 patient years of exposure) or the placebo group (2266 patient years of exposure). A post-hoc meta-analysis of death from any cause that occurred in these 4 trials was conducted to evaluate the risk of mortality of Spiriva Respimat once-daily 5mcg (SR 5mcg) compared with placebo. The analysis using a stratified Cox regression model found the incidence of all-cause mortality to be higher in the SR 5mcg group (68 deaths; incidence rate: 2.6 per 100 patient years) compared to the placebo group (51 deaths; incidence rate: 2.0 per 100 patient years) (Table 2). The result is not statistically significant [HR (95% CI): 1.33 (0.92 – 1.90)]. The finding of an increase in mortality in the VSD is not consistent with that of TIOSPIR, when taking into consideration of a third source of mortality data obtained from a 4-year, randomized, placebo-controlled, parallel group study UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium, Study 205.235).

UPLIFT randomized nearly 6000 subjects with moderate-severe COPD to either a Spiriva HandiHaler 18 mcg (SHH 18mcg) group or a placebo group. UPLIFT provided a substantial amount of controlled long-term safety data for Spiriva HandiHaler. In this study, data on deaths, including the vital status of subjects who withdrew from the study, were collected prospectively, and the cause of death was adjudicated in a blinded fashion by an independent committee. By the planned end of the study at Day 1440, vital status was confirmed for 95% of all randomized subjects. A total of 921 deaths were collected by Day 1440, with 491 deaths reported in the placebo group (incidence rate: 4.5 per 100 patient years) while 430 deaths were reported in the HandiHaler arm (incidence rate: 3.9 per 100 patient years). The data on cardiovascular risk and mortality from UPLIFT was thoroughly reviewed by the Agency, and discussed in a FDA

meeting of the Pulmonary–Allergy Drugs Advisory Committee (PADAC) on November 19, 2009. Overall, UPLIFT did not show increased risk of mortality [HR (95% CI): 0.87 (0.76, 0.99)], stroke, cardiovascular (CV) death and myocardial infarction (MI) with Spiriva HandiHaler relative to placebo.

While the integrated placebo-controlled vital status database showed a statistically non-significant risk increase in the Spiriva Respimat 5 mcg arm, compared with placebo, the amount of information provided in this database is relatively small compared to UPLIFT and TIOSPIR (Table 2). It is possible that the elevated mortality risk is a chance finding due to an unusually low incidence rate of deaths observed in the pooled placebo arm of the vital status database. Combining the two large-scale, long-term, well designed and conducted studies TIOSPIR and UPLIFT, the data is convincing on a comparable mortality of Spiriva Respimat 5mcg daily to Spiriva HandiHaler 18 mcg daily, as well as to placebo.

There are lingering signals about fatal myocardial infarction observed in the VSD (2 in placebo arm, 9 in Respimat 5mcg arm) and TIOSPIR (3 in HandiHaler arm, 11 in Respimat 5mcg arm). The small number of events makes it hard to interpret such findings, especially when overall mortality is reassuring and there are no signals with overall MACE in both TIOSPIR and the VSD (refer to Section 3). It makes the interpretation even harder while UPLIFT showed no risk increase in stroke, MI, or CV death associated with Spiriva HandiHaler.

Overall, this NDA resubmission resolved the safety concerns listed in the Complete Response Letter issued on September 16, 2008. The data showed no evidence of increased risk of all-cause mortality associated with the use of Spiriva Respimat compared to Spiriva HandiHaler, for which the safety profile was well-established through a large-scale and long-term study UPLIFT. A drug approval is recommended for Spiriva Respimat 5 mcg once daily based on the data included in the NDA resubmission, from a statistical perspective.

Table 2: Summary of Mortality Data from UPLIFT, TIOSPIR and the VSD

	UPLIFT		**TIOSPIR**		**Vital Status Database**	
Treatment	**Placebo**	**SHH 18mcg**	**SHH 18mcg**	**SR 5mcg**	**Placebo**	**SR 5mcg**
N	3006	2986	5694	5711	3047	3049
Total V/S F/U*, yrs	10872	10927	13050	13135	2571	2574
Deaths	491	430	439	423	51	68
IR per 100 PYs	4.5	3.9	3.4	3.2	2.0	2.6
HR (95% CI)		**0.87 (0.76, 0.99)**		**0.96 (0.84, 1.09)**		**1.33 (0.93, 1.92)**

Source: Created by reviewer.

*: V/S F/U = vital status follow up

2 INTRODUCTION

2.1 Overview

This NDA is submitted in support of Spiriva (tiotropium bromide) inhalation spray delivered via the Respimat device. The proposed trade name is Spiriva Respimat.

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

The initial NDA for SPIRIVA RESPIMAT was submitted on November 16, 2007. The Agency issued a Complete Response Letter on September 16, 2008, which concluded that this application could not be approved in its present form. Specifically, two clinical deficiencies were identified by the Division of Pulmonary, Allergy and Rheumatology Products (DPARP), along with guidance on what would be required to resolve the deficiencies:

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

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

2. *The submitted data do not provide substantial evidence to support the proposed claim of reduction of COPD exacerbation. While the pre-specified combined analysis of the two 48-week clinical studies 205.254 and 205.255 show a decreased number of COPD exacerbations with Spiriva Respimat compared to placebo, replication of the finding is necessary to support a labeling claim. Results of the two 48-week studies are not sufficient for replication because only one of the two studies showed a*

statistically significant difference from placebo. The clinical study 205.266 is not acceptable for replication because the study was conducted with Spiriva HandiHaler, which is a distinct product in terms of efficacy.

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

Boehringer Ingelheim (BI) resubmitted the NDA 21-936 on March 24, 2014. In the NDA resubmission, BI provides the following updates to Module 5 "Clinical Study Reports":

> **Module 5**: The principal update to the clinical portion of this resubmission includes three new trials: the long-term, active-controlled TIOSPIR study 205.452 in which SPIRIVA RESPIMAT was compared to SPIRIVA HANDIHALER, the pharmacokinetics (PK) trial 205.458, and the 1-year placebo-controlled study 205.372 that provides the efficacy and safety results of SPIRIVA RESPIMAT versus placebo.

The applicant seeks to address the question on fatal events primarily based on the information derived from the new long-term clinical study 205.452 (TIOSPIR). TIOSPIR is a multi-center, multi-national, double-blind, comparative trial evaluating the safety and efficacy of two doses of Spiriva Respimat (once-daily 2.5 or 5mcg) (SR 2.5mcg or SR 5mcg), compared with Spiriva HandiHaler (once-daily 18mcg) (SHH 18mcg). TIOSPIR is a large-scale, event-driven, non-inferiority trial which was designed and powered to rule out a 25% or higher excess risk of all-cause mortality in the Respimat groups (SR 2.5mcg or SR 5mcg) relative to the HandiHaler group. Per the study protocol, participating clinical sites were to follow all randomized subjects for vital status until trial conclusion, including subjects who prematurely discontinued study medication, and collect medical information regarding the date and cause of fatal events. TIOSPIR has two pre-defined primary endpoints: time to all-cause mortality and time to first COPD exacerbation. This review will focus on evaluation of safety therefore will not review the COPD exacerbation endpoint, which is evaluated in the statistical efficacy review by Dr. Kiya Hamilton.

In the NDA resubmission additional supplemental data on mortality was submitted in a so-called placebo-controlled vital status database (VSD) which integrates the vital status information from four randomized, double-blind, placebo-controlled Respimat clinical trials with a parallel group design of at least 24 weeks duration. These include three Phase 3 exacerbation trials (Studies 205.254, 205.255 from the original NDA and a more recent trial, Study 205.372) and one Phase 3 bronchodilation trial (Study 1205.14). In these efficacy trials of Spiriva Respimat, vital status information was followed and collected either retrospectively or prospectively. The applicant conducted a post-hoc meta-analysis of death from any cause that occurred in these 4 trials to

evaluate the risk of mortality of Spiriva Respimat once-daily 5mcg (SR 5mcg) compared with placebo.

The summary of design characteristics of TIOSPIR and the 4 studies included in the VSD is presented in Table 3. This information is utilized in the evaluation of mortality which is the subject of this statistical review.

Table 3: Summary of Design Characteristics of TIOSPIR and the 4 Randomized Phase 3 Trials Included in the Mortality Meta-Analysis of the Vital Status Database (VSD)

Trial	Treatment Arms	Number of Randomized Subjects	Duration	Vital Status Follow-up until Trial Completion
205.452 (TIOSPIR)	SHH 18mcg SR 2.5mcg SR 5mcg	5713 5741 5729	Event-driven	Pre-specified
Vital Status Database (VSD)				
202.254*	Placebo SR 5mcg SR 10mcg	319 332 332	48-week	Retrospectively collected for discontinued subjects
202.255*	Placebo SR 5mcg SR 10mcg	334 338 335	48-week	Retrospectively collected for discontinued subjects
202.372	Placebo SR 5mcg	2002 1989	48-week	Pre-specified
1205.14	Placebo BEA 50mcg BEA 100mcg BEA 200mcg SR 5mcg	429 419 415 390 427	24-week	Pre-specified

Source: Created by reviewer.

* Pivotal efficacy trials included in original NDA submission of Spiriva Respimat.

2.2 Data Sources

The applicant submitted electronic documents and datasets for TIOSPIR and the VSD. The applicant's study reports were used for comparison and verification purpose. The materials are archived in the CDER Electronic Document Room (EDR). The below materials were utilized in the evaluation of safety of Spiriva Respimat.

Study Report \\cdsesub1\evsprod\NDA021936\0003\m5\53-clin-stud-rep\535-rep-effic-safety-stud\copd\5351-stud-rep-contr\0205-0452\0205-0452--01-15--study-report-body.pdf
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IR Response

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Analysis Data Sets

(Adverse Events)

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(Subject Level)

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(Disposition)

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3 STATISTICAL EVALUATION

This review is focused on the assessment of mortality and cardiovascular events in the Spiriva Respimat application generated from TIOSPIR comparing Respimat to HandiHaler, and a meta-analysis of placebo-controlled efficacy trials comparing Spiriva Respimat 5mcg to placebo.

3.1 Data and Analysis Quality

Data and reports of this submission were submitted electronically. The data define file provides sufficient information about the variables included in each dataset. Using the submitted data, the reviewer was able to perform all analyses and reproduce the major findings included in the study reports. No major data quality issues were identified.

3.2 Evaluation of Efficacy

This review does not evaluate efficacy submitted to the NDA. The reader is referred to the statistical review by Dr. Kiya Hamilton.

3.3 Evaluation of Safety

3.3.1 Study 205.452 - TIOSPIR

3.3.1.1 Study Design and Endpoints

3.3.1.1.1 Study Design

TIOSPIR was a randomized, double-blind, active-controlled, double-dummy, parallel group, multi-center trial to compare the efficacy and safety of 2.5 mcg and 5 mcg tiotropium inhalation

solution delivered by the Respimat Inhaler with tiotropium inhalation capsules 18 mcg delivered by the HandiHaler device.

***Reviewer's Comment**: The choice of control group as Spiriva HandiHaler was driven by findings from the UPLIFT trial. UPLIFT was a four year safety and efficacy trial that compared Spiriva HandiHaler to placebo. Nine hundred twenty-one deaths were observed in 5992 subjects randomized in UPLIFT (491 deaths out of 3006 randomized placebo subjects and 430 deaths out of 2986 randomized HandiHaler subjects). The resulting estimated HR was 0.87 with 95% confidence interval of (0.76, 0.99). For a detailed statistical review of UPLIFT please refer to the review authored by Dr. Joan Buenconsejo on 12/04/2009.*

In TIOSPIR, a total of 17,183 subjects were randomized in a 1:1:1 ratio to 2.5 mcg tiotropium inhalation solution delivered by the Respimat Inhaler (SR 2.5mcg), 5 mcg tiotropium inhalation solution delivered by the Respimat Inhaler (SR 5mcg) and tiotropium inhalation capsules 18 mcg delivered by the HandiHaler Inhaler (SHH 18mcg). TIOSPIR was conducted at 1202 centers in a total of 50 countries, in male and female outpatient COPD subjects of at least 40 years of age. TIOSPIR was conducted from May 14, 2010 until its completion date on May 23, 2013.

The statistical design was based on demonstrating non-excessive risk (i.e. non-inferior) of death in the Respimat arm relative to the HandiHaler arm. The null hypothesis was that there is 25% or higher excess risk of all-cause mortality in the Respimat group relative to the HandiHaler group. The study was powered under a one-sided alternative hypothesis, in which Respimat was non-inferior to HandiHaler, assuming a hazard ratio (HR) of 1 or less. To achieve at least 90% power to rule out a risk margin of 1.25, it was necessary to observe at least 1,266 deaths.

This event-driven trial was designed to continue until 1,266 deaths were reported[1]. The trial consisted of a screening visit to assess subject eligibility. Following screening, the subject was randomized into the double-blind treatment portion of the study (Visit 1) in which they received one of the three tiotropium treatments (SR 2.5mcg, SR 5mcg or SHH 18mcg). All subjects also received placebo concurrent with active treatment per the double dummy design. After the randomization visit, visits were scheduled at 6 weeks and 12 weeks and every 12 weeks thereafter (with interim contacts required 6 weeks after each visit, preferably by telephone) until the event-driven end of the trial. All subjects were to remain in the trial until study closeout; the majority of subjects were on study medication between 2 and 3 years. One follow-up contact (preferably telephone call) was conducted 30 days after the last dose of study medication. Subjects who discontinued study medication prematurely continued to be followed every 12 weeks for vital status information until the event-driven end of the trial. The study timeline is shown in Table 4.

[1] With a recritment period of 11 months and subjects follow-up time between 2 and 3 years, the actual number of observed deaths in TIOSPIR was 1302.

Table 4: Study Timeline

		Treatment Period						Follow up
Visit Number	**0**	**1**	**2**	**3**	**Interim contact***	**4 to *Last treatment visit***	***End of treatmen***	
Visit Time	Visits 0 and 1 may occur on the same day in some cases	Week 0 (Maximum 4 weeks from Visit 0)	Week 6 (± 7 days)	Week 12 (± 7 days)	Week 18 (± 7 days) and 6 weeks after each treatment visit (Weeks 30, 42, 54, 66, 78, 90, 102, 114, 126, 138, 150, 162, 174)	Week 24 and every 12 weeks (± 14 days) thereafter (Weeks 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180)	*Variable depending on event driven end of trial*	(30 ± 3 days)

Source: Sponsor's clinical study report.
*: A personal contact (preferably telephone) took place between each treatment visit. The PI or designee contacted the subject and collected information regarding COPD exacerbation status, concomitant medication status, and adverse events. For subjects who discontinued trial medication, a personal contact was made every 12 weeks.

3.3.1.1.2 Endpoints

Per the Statistical Analysis Plan (SAP), the first pre-specified primary endpoint is time to all-cause mortality. The second primary endpoint is time to first COPD exacerbation. This review will focus on evaluation of safety therefore will not review the COPD exacerbation endpoint, which is evaluated in the statistical review of Dr. Kiya Hamilton.

The secondary safety endpoints included specific protocol-defined outcome events:

- Time to onset of first major adverse cardiovascular event (MACE)
- Time to death from MACE

The composite endpoint MACE is defined as:

- Fatal event in the MedDRA system organ classes (SOC) of cardiac and vascular disorders
- MedDRA Preferred terms: sudden death, cardiac death, sudden cardiac death
- Outcome events of stroke (serious and non-serious)
- Outcome events of myocardial infarction (MI) (serious and non-serious)
- Outcome events of transient ischemic attack (TIA) (serious and non-serious)

Additional endpoints that will be analyzed are:

- Time to onset of first stroke (outcome event)
- Time to onset of first MI (outcome event)
- Time to onset of TIA (outcome event)

The definitions of the protocol-defined adverse events are:

- Stroke: defined as an acute onset of focal neurological deficit of presumed vascular origin lasting for 24 hours or more or resulting in death. Additionally, an event lasting <24 hours will be considered as a stroke if this is due to: 1) therapeutic intervention by pharmacological or non-pharmacological means (i.e., thrombolytics, intracranial

angioplasty), or 2) brain imaging available early clearly documents a new hemorrhage or infarct. Fatal stroke is defined as death from any cause within 30 days of stroke.

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

  2) Sudden unexpected cardiac death, including cardiac arrest, with symptoms suggestive of myocardial ischemia, accompanied by new ST elevation, or new LBBB, or definite new thrombus by coronary angiography but dying before blood samples could be obtained, or in the lag phase of cardiac biomarkers in the blood.
  3) For percutaneous coronary intervention (PCI) in patients with normal baseline values, elevations of cardiac biomarkers above 99th percentile of the URL are indicative of per-procedural myocardial necrosis.
  4) For coronary artery bypass graft (CABG) in patients with normal baseline values, elevations of cardiac biomarkers above the 99th percentile of the URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 5 x 99th percentile of the URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related MI.
  5) Pathological findings post-mortem of an acute MI.
- Transient Ischemic Attacks: defined as a rapid onset of a focal neurological deficit that resolves spontaneously without evidence of residual symptoms at 24 hours.

Reviewer's Comment*: MACE events were not adjudicated by an independent committee. Also, TIOSPIR was not powered to formally assess MACE-related safety endpoints. Of note, the definition of MACE is not exactly same as the standard definition used in many cardiovascular outcome trials (CVOT).*

3.3.1.1.3 Events Collection and Classification

Adverse events having occurred during the course of the trial were collected, documented and reported to the sponsor by the investigator on the appropriate case report form (CRF)(s) or eCRFs or SAE reporting forms, according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the Investigator Site File. For each event, the investigator will provide the onset date, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug. The investigator will determine the relationship of the investigational drug to all events. The investigator was also responsible to report AEs occurring within the 30 days after a subject completed the trial in the eCRF. SAEs

and non-serious AEs must include a causal relationship assessment made by the investigator. All SAEs should be entered into the eCRF. For the assessment of all-cause mortality, subjects who discontinued study medication prematurely were contacted every 12 weeks to obtain vital status information until the event-driven end of the study.

An independent mortality adjudication committee (MAC) adjudicated all deaths in the trial. The purpose of the MAC was to provide a consistent, blinded, independent evaluation of deaths in order to determine primary cause of death for purposes of safety evaluation of mortality endpoints in this trial. All deaths were adjudicated to determine a single cause of death for deaths reported at least ten days prior to database lock (for deaths reported within ten days of database lock, the cause determined by investigator was used). These adjudicated causes of death were used to define cardiovascular deaths in the MACE endpoint and also in supportive analyses in primary and secondary endpoints.

3.3.1.2 Statistical Methodologies

This NDA submission included a statistical analysis plan which was finalized on June 11, 2013 with documented pre-specified statistical methods.

Reviewer's Note: *Neither the SAP nor statistical analysis portions of the protocol for TIOSPIR were reviewed prior to trial initiation.*

3.3.1.2.1 Hypothesis Testing

Per the SAP, the following hypothesis for all-cause mortality would be tested at the end of the study for SR 5mcg vs. SHH 18mcg:

H_0: HR $\geq$ 1.25; vs. H_a: HR < 1.25

If the upper bound of the 95% confidence interval of the hazard ratio estimate excluded values of 1.25 or higher, it would be concluded that no meaningful excess risk associated with Respimat 5 mcg treatment was observed, compared to HandiHaler 18 mcg treatment. If the upper confidence bound was at or above 1.25, the null hypothesis of a meaningful excess risk associated with SR 5mcg use would not be rejected.

If the excessive risk hypothesis is rejected for SR 5mcg, the testing will hierarchically proceed to a comparison of SR 2.5mcg vs. SHH 18mcg to rule out a relative 25% risk increase of all-cause mortality for this lower dose with the same device. If the upper bound of the 95% confidence interval excluded values of 1.25 or higher, it would be concluded that no meaningful excess risk is associated with Respimat 2.5 mcg treatment compared to HandiHaler 18 mcg treatment. If the upper confidence bound was at or above 1.25, the null hypothesis of a meaningful excess risk in SR 2.5mcg would not be rejected.

3.3.1.2.2 Analysis Methods

3.3.1.2.2.1 Analysis Populations and Event Ascertainment

The safety evaluation involving mortality utilizes an analysis population (Death Analysis Set, DAS) which consists of all randomized subjects who received at least one dose of blinded study medication. For all other analyses reported in this review, the analysis set (Treated Set, TS) excluded 19 subjects with potential data irregularities from the DAS since only vital status data were considered reliable for these subjects.

Subjects who prematurely discontinued medication were followed until the end of the trial for vital status. For the primary analysis of time to death from any cause, an "on-study" censoring scheme is utilized for event ascertainment. The on-study censoring scheme includes all deaths that occurred during the course of the study (active treatment period + off-treatment vital status follow-up period). For the time to death endpoint, subjects who were lost to follow-up or had no death reported were censored at the time of their last known vital status.

- Deaths are counted whenever they arise from the corresponding fatal AE that has an onset date on or after date of first dose of randomized treatment and an end date prior to the end of the trial.
- Time to death is defined as time (in days) from the first administration of randomized treatment to the end date of a fatal AE (i.e., date of death). Subjects without a fatal event will be censored at the last date for which they were known to be alive.
- For incidence rates, time at risk is calculated as follows:
  = Death date - date of first administration of randomized treatment + 1 (for subjects with a fatal event)
  = Date last known alive - date of first administration of randomized treatment + 1 (for subjects with no fatal event)

A planned sensitivity analysis was included that utilizes an "on-treatment" censoring scheme that includes all fatal adverse events (FAE) that occurred during the actual treatment period plus 30 days post treatment (on-treatment analysis of FAE). The details of event ascertainment and time at risk calculation are listed below.

- Fatal events are counted whenever they have an onset date between date of first dose of randomized treatment and date of last dose of randomized treatment + 30 days.
- Time to fatal adverse event is defined as time (in days) from the first administration of randomized treatment to the onset date of the fatal AE. Subjects without a fatal event will be censored at the day of last administration of treatment + 30 days.
- For incidence rates, time at risk is calculated as follows:
  = Fatal AE onset date - date of first administration of randomized treatment + 1 (for subjects with a fatal event)
  = Min (Date of last administration of randomized treatment + 30 days, last known vital status) - date of first administration of randomized treatment + 1 (for subjects with no fatal event)

3.3.1.2.2.2 Primary Endpoint Analysis

The pre-specified primary analysis of time to death from any cause was evaluated through a Cox proportional hazards regression model with treatment group as the only covariate. Estimated hazard ratios and corresponding 95% confidence interval of the association between treatment and risk of all-cause mortality will be reported in this review. The proportional hazards assumption of the Cox model will be evaluated graphically by plotting the log-log survival curve and the Schoenfeld residuals against time.

3.3.1.2.2.3 Additional Sensitivity Analyses on Primary Endpoint by Review (On-treatment Analysis of Death)

To study the impact of excluding deaths reported from the post active treatment follow-up period, this review calculated the hazard ratio and corresponding 95% CI of occurrence of the primary events of interest – death from any cause, based on the following censoring scheme:

- Deaths are counted whenever they arise from the corresponding fatal AE that has an onset date on or after date of first dose of randomized treatment and an end date (i.e., date of death) prior to date of last dose of randomized treatment + 30 days.
- Time to death is defined as time (in days) from the first administration of randomized treatment to the end date of a fatal AE (i.e., date of death). Subjects without a fatal event will be censored at the day of last administration of treatment + 30 days.
- For incidence rates, time at risk is calculated as follows:
  = Fatal AE death date - date of first administration of randomized treatment + 1 (for subjects with a fatal event)
  = Min (Date of last administration of randomized treatment + 30 days, last known vital status) - date of first administration of randomized treatment + 1 (for subjects with no fatal event)

The difference between this sensitivity analysis and the sponsor's sensitivity analysis are: 1) it does not count the fatal events which had an end date (i.e. death date) later than 30 days post-treatment as an on-treatment death; 2) time-to-event calculation is based on the date of death (i.e. the end date of an fatal adverse event) instead of the onset date of an fatal adverse event.

3.3.1.2.2.4 Adjudicated Cause of Death

Adverse events were coded using the MedDRA coding dictionary version 16.0. The frequency of subjects with adjudicated primary cause of death was summarized by treatment, primary system organ class (SOC) and preferred term (PT), and also by treatment, pharmacovigilance (PV) endpoint/standardized MedDRA query (SMQ), and PT.

3.3.1.2.2.5 Secondary Endpoints Analysis

As pre-specified in the SAP, time-to-event analysis was planned to be performed for the following secondary endpoints.

- Time to onset of first MACE: on-treatment analysis. Subjects without an observed MACE event were censored at the time of treatment discontinuation plus 30 days (or date of last known vital status if subject died or lost to follow up before that).
- Time to death from MACE: on-study analysis. Events include all deaths determined by adjudication to be due to MACE. Subjects without an observed event were censored at the time of their last known vital status.

For these secondary endpoints, a similar Cox proportional hazards model, as that used for the analysis of the primary endpoint, was used to calculate the hazard ratio and its corresponding nominal 95% CI comparing Respimat 5mcg to HandiHaler 18mcg, and Respimat 2.5mcg to Handidaler 18mcg, respectively. No multiplicity adjustments were planned for the analyses of secondary endpoints.

3.3.1.3 Subject Disposition, Demographic and Baseline Characteristics

Overall, 20,313 subjects were enrolled in TIOSPIR. Among these, 17,183 (RS) were randomized to one of three tiotropium treatments: 5741 subjects were randomized to receive SR 2.5mcg, 5729 subjects were randomized to receive SR 5mcg, while 5713 subjects were randomized to receive SHH 18mcg. Forty-eight of the randomized subjects did not receive study medication (46 subjects did not receive trial medication and 2 subjects were double randomized). Using an intention-to-treat (ITT) approach, the remaining 17,135 subjects (DAS analysis population) were followed for vital status for the duration of the trial, regardless of whether the subject prematurely discontinued study medication. The DAS was used for the analyses of all mortality endpoints, including the primary safety endpoint of time to death, the sensitivity analysis of on treatment fatal adverse events, and all secondary mortality endpoints, including summarization of all adjudicated deaths (by SOC and PT) and time to death from MACE. Audit findings from Site 1280 and Site 49157 identified data irregularities which affected data obtained from 19 randomized subjects in the trial. Thus data from these 19 out of the 17,135 randomized subjects were excluded from specific planned analysis (all demographics and baseline characteristics, summarization of all non-fatal AEs including protocol-defined outcome events and components of the composite endpoint of MACE, all non-fatal SAEs, all AEs that led to discontinuation of study medication, and all investigator-determined drug-related AEs). As a result, the treated set (TS) comprised 17,116 subjects.

Based upon Table 5, we observed no noticeable imbalances in baseline characteristics across the three treatment groups in TIOSPIR. There were more male subjects than female subjects (72% versus 28%). Approximately 82% of subjects were White, about 14% were Asian, and about

1.5% were Black or African American. Race information was missing for 468 subjects (3%) from France where race cannot be collected as well as 1 subject from Peru whose race was determined to be Mestizo. By region, the highest number of subjects were randomized in the Europe/Africa/Australia/New Zealand region (56.3%), followed by North America (24.1%), Asia (13.8%), and Latin America (5.8%). About 21% of subjects were randomized in the United States. The mean age was around 65 years. The mean baseline body mass index (BMI) was about 26.2 kg/m^2. In the treated set, about 62% and 38% of subjects were former and current smoker, respectively, with a mean smoking history of 43.8 pack years. The mean duration of COPD was 7.4 years.

Overall, 10.7% of all treated subjects had a history of cardiac arrhythmia at baseline and 15.2% of all treated subjects had a history of ischaemic heart disease/coronary artery disease. The incidence of subjects who reported a medical history of MI, stroke or TIA was 6.0%, 2.3%, and 1.4%, respectively. Medical history, including history of cardiovascular and COPD events, was generally similar across the three treatment groups at baseline. The majority of all treated subjects (90.6%) were receiving pulmonary medications at baseline. The overall incidence of pulmonary medication use at baseline was balanced across treatments. At baseline, 46.9% of subjects reported concomitant use of inhaled long-acting anticholinergics, 61.8% reported concomitant use of long-acting beta-agonists (LABAs), 53.6% of subjects were taking inhaled short-acting beta adrenergics, and 59.0% of subjects reported concomitant use of inhaled corticosteroids (ICS). Approximately half of all treated subjects (51.1%) were receiving cardiac medications (excluding statins, which were not collected) at baseline. The rate of cardiovascular medication use at baseline was balanced across the three tiotropium treatments.

Table 5: Demographics and Baseline Characteristics by Treatment Group (TS)

	SHH 18mcg (N = 5687)	SR 2.5mcg (N = 5724)	SR 5mcg (N = 5705)
Age (yrs), mean±SD	65.0±9.0	65.1±9.1	64.9±9.1
Sex, % Female	29.0%	28.9%	27.5%
Race			
White	81.4%	81.8%	81.5%
Black	1.5%	1.3%	1.6%
Asian	14.3%	14.2%	14.1%
Missing	2.7%	2.7%	2.8%
Region			
North America, US	20%	21%	21%
North America, non-US	3%	3%	3%
Latin America	6.0%	5.8%	5.7%
Euro/Africa/Aus/NZ	56.2%	55.9%	56.8%
Asia	14.0%	13.8%	13.6%
BMI (kg/m²), mean±SD	26.2±5.7	26.2±5.7	26.2±5.7
Current smoker, %	37.7%	37.9%	38.7%
Smoking history (pk yrs), mean±SD	43.7±24.7	43.6±24.6	44.1±25.0
Duration of COPD (yrs), mean±SD	7.5±6.2	7.4±6.1	7.4±6.2
Medical history at baseline (%)			
MI	6.1%	5.9%	5.9%
Stroke	2.2%	2.2%	2.4%
Cardiac arrhythmia	10.7%	10.6%	10.8%
Ischemic heart disease/ CAD	15.7%	14.8%	15.0%
Use of any respiratory med. (%)	90.7%	90.8%	90.3%
LABA	62.3%	61.9%	61.2%
Use of any cardiac med. (%)	50.8%	51.7%	50.9%

Source: Created by reviewer.

An overview of subject disposition by treatment group is summarized in Table 6. As summarized in Table 4, approximately 77.1% of subjects (13,199/17,116) completed treatment in TIOSPIR, while 22.9% of subjects (3917/17116) prematurely discontinued study medication. The rate of premature discontinuation from trial medication was comparable across the three treatment groups: 22.6% in the SHH 18mcg group, 23.1% in the SR 2.5mcg group, and 22.9% in the SR 5mcg group. The three most common reasons for early discontinuation were adverse events (10.8%), subject refusal to continue taking trial medication (5.8%), and "other" (3.3%), where "other" included, but was not limited to, subject no longer willing or able to participate in trial, inclusion or exclusion criteria not met after randomization, subject moved, site closure by sponsor, and personal or family reasons. The rate of the remaining reasons for premature discontinuation was less than 2%. The subject dispositions are generally similar across the three treatment arms.

Table 6: Subject Disposition

	SHH 18mcg	SR 2.5mcg	SR 5mcg	Total
All randomized (RS)	**5713**	**5741**	**5729**	**17183**
Death Analysis Set (DAS)	**5694**	**5730**	**5711**	**17135**
Vital Status Complete	5678	5713	5697	17088
Treated Set (TS)	**5687 (100%)**	**5724 (100%)**	**5705 (100%)**	**17116 (100%)**
Completed treatment	**4400 (77.4%)**	**4400 (76.9%)**	**4399 (77.1%)**	**13199 (77.1%)**
Discontinued treatment	**1287 (22.6%)**	**1324 (23.1%)**	**1306 (22.9%)**	**3917 (22.9%)**
Adverse event	11.2%	10.5%	10.6%	10.8%
AE study dis. Worse	3.3%	3.0%	3.0%	3.1%
AE other dis. Worse	1.0%	0.8%	0.8%	0.9%
AE other	6.9%	6.7%	6.8%	6.8%
Protocol violation	0.7%	1.1%	1.2%	1.0%
Lack of efficacy	1.0%	1.1%	1.1%	1.1%
Refused cont. medic.	5.6%	5.8%	5.9%	5.8%
Lost to follow-up	1.0%	0.9%	1.1%	1.0%
Other	3.1%	3.7%	3.1%	3.3%

Source: Created by reviewer.

Per protocol, subjects who prematurely discontinued study medication for any reason were to be followed every 12 weeks for vital status information until the event-driven end of the study. Details of subject vital status follow up are summarized in Table 7. Overall, the majority of subjects that were eligible for follow up of vital status were followed for two to three years: 89.2% of subjects were followed for 24 to 36 months. The distribution of vital status observation time are well balanced within the three tiotropium treatment groups, with a mean follow-up time of 838.2 days in the total population. For the analysis of incidence of death, the total person time of follow-up (or observation) is defined as the sum over all DAS subjects of (date last known alive – randomization date + 1) / 365.25. The total person years of follow-up/observation for the three treatment groups are similar. At the end of the study, vital status was confirmed for 99.7% of all eligible randomized subjects (N = 17135), with a lost to follow-up rate of about 0.3%.

Table 7: Subject Vital Status Follow Up (DAS)

	SHH 18mcg	SR 2.5mcg	SR 5mcg	Total
Death Analysis Set (DAS)	**5694 (100%)**	**5730 (100%)**	**5711 (100%)**	**17135 (100%)**
Vital status Confirmed	**5678 (99.7%)**	**5713 (99.7%)**	**5697 (99.8%)**	**17088 (99.7%)**
Alive	92.0%	92.0%	92.3%	92.1%
Died	7.7%	7.7%	7.4%	7.6%
Lost to follow-up	**0.3%**	**0.3%**	**0.2%**	**0.3%**
Days of vital status follow-up				
Mean (SD)	837.1 (146.5)	837.3 (147.2)	840.1 (141.2)	838.2 (145.0)
Median	869.0	869.0	870.0	869.0
Min, Max	9, 1094	3, 1077	18, 1081	3, 1094
Total observation time, yrs	**13050.2**	**13135.3**	**13135.1**	**39320.7**
0-12 months	2.7%	2.7%	2.4%	2.6%
12-24 months	8.7%	8.1%	7.9%	8.2%
24-36 months	88.7%	89.2%	89.7%	89.2%

Source: Created by reviewer.

An overview of treatment exposure is summarized in Table 8. A total of 17116 subjects (excluding those 19 subjects from Sites 1280 and 49157) received at least one dose of study medication and were included in the treated set. The mean exposure was similar among the three active treatment groups: 728.1 days in the SHH 18mcg group, 727.8 days in the SR 2.5mcg group, and 726.2 days in the SR 5mcg group, respectively. The median exposure was 835 days in all three treatment groups, with an overall maximum exposure of 1027 days.

The majority of subjects (76.8%) achieved the anticipated duration of exposure to study drug estimated to be between 2 to 3 years. The overall duration of exposure to tiotropium was 34084.8 patient years, which comprises 11336.7 patient years in the SHH 18mcg group, 11405.0 patient years in the SR 2.5mcg group, and 11343.1 patient years in the SR 5mcg group.

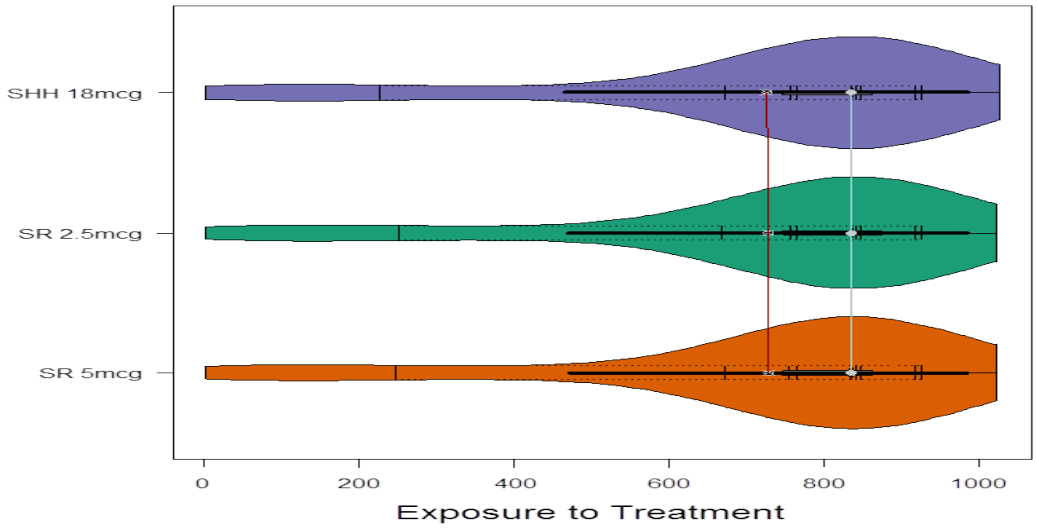
Table 8: Extent of Exposure by Treatment Group (TS)

	SHH 18mcg	SR 2.5mcg	SR 5mcg	Total
Treated Set (TS)	**5687**	**5724**	**5705**	**17116**
Days on Treatment				
Mean (SD)	728.1 (255.0)	727.8 (256.1)	726.2 (258.7)	727.4 (256.6)
Median	835.0	835.0	835.0	835.0
Min, Max	1, 1023	1, 1022	1, 1027	1, 1027
Total time on treatment, yrs	**11336.7**	**11405.0**	**11343.1**	**34084.8**

Source: Created by reviewer.

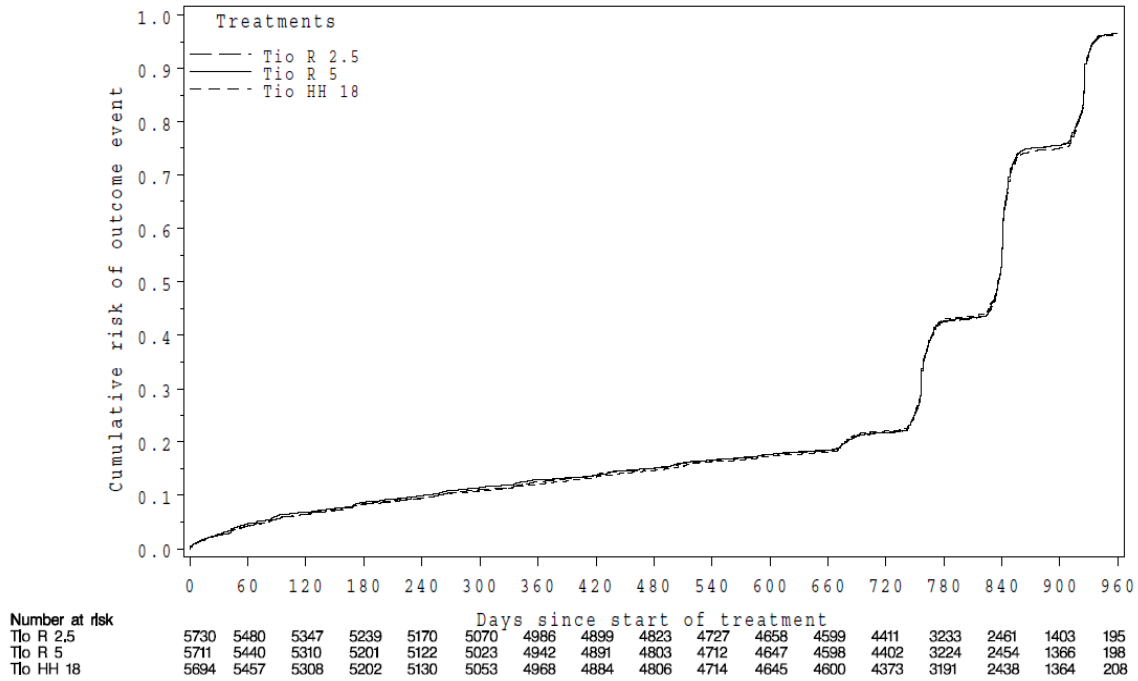
As shown in Figure 1 and Figure 2, the distribution of treatment exposure (or patterns of treatment discontinuation) were similar across the three groups. These observations are consistent with the balanced rate of premature discontinuation of study medication observed across treatments during the study (Table 6).

Figure 1: Violin Plot of Distribution of Treatment Exposure by Treatment Group (in days)



Source: Created by reviewer.

Figure 2: Kaplan-Meier Plot of Time to Early Treatment Discontinuation (in days)



Source: Sponsor's clinical study report. Tio R 2.5 = SR 2.5mcg; Tio R 5 = SR 5mcg; Tio HH 18 = SHH 18mcg.

3.3.1.4 Results and Conclusions

3.3.1.4.1 Primary Endpoint Analysis

The primary endpoint was the time from the first drug date to death from any cause. Table 9 summarizes the primary event information and the primary analysis results, along with the sensitivity analysis results using alternative censoring schemes to study the impact of excluding deaths collected during the post-treatment vital status follow-up..

There were 439 (7.7%) death events observed in the SHH 18mcg arm, which corresponds to an incidence rate of 3.4 per 100 patient years, based on a total of 13050.2 patient years of follow-up in the HandiHaler arm. There were 440 (7.7%) observed death events during 13135.3 patient years of follow-up in the SR 2.5mcg arm, corresponding to an incidence rate of 3.3 per 100 patient years. The incidence rate of death from any cause was 3.2 per 100 patient years in the SR 5mcg group, with 423 deaths reported during a total of 13135.1 patient years of follow-up.

The pre-specified Cox proportional hazards model was used to evaluate the risk of death associated with Respimat use, when compared with HandiHaler device. Based on this model, the estimated hazard ratio of death for SR 5mcg vs. SHH 18mcg is 0.96 with 95% confidence interval (0.84, 1.09). It demonstrates that SR 5mcg is not associated with elevated risk of all-cause mortality based upon the pre-specified risk margin of 1.25.

Per the pre-specified hierarchical testing strategy, the same model was employed to evaluate the risk of death associated with the lower dose Respimat 2.5mcg when compared with HandiHaler.

The estimated HR for SR 2.5mcg versus SHH 18mcg was 1.0 with 95% CI (0.87, 1.14). The risk margin of 1.25 is also excluded for the comparison of SR 2.5mcg to SHH 18mcg.

The results are consistent when using alternate event and event censoring schemes. When considering fatal adverse events with "on-treatment + 30 days" ascertainment window, 357 events were observed in the SHH 18mcg group while 359 and 326 events were observed in the SR 2.5mcg group and SR 5mcg group, respectively. The point estimate of the HR for SR 5mcg vs. SHH 18mcg is 0.91, which is close to that of the primary analysis, with a 95% CI of (0.79, 1.06). The point estimate of the HR for SR 2.5mcg vs. SHH 18mcg is 1.0, with a 95% CI of (0.86, 1.16). When considering deaths with the censoring window of "on-treatment + 30 day", 299 deaths were observed in the SHH 18mcg group while 321 and 284 deaths were observed in the SR 2.5mcg group and SR 5mcg group, respectively. Similarly, a HR estimate of 0.95 with 95% CI of (0.81, 1.12) was found for the comparison SR 5mcg vs. SHH 18mcg. For SR 2.5mcg vs. SHH 18mcg, the HR estimate is 1.07, with a 95% CI of (0.91, 1.25)

Reviewer's Comment: *The graphical check in Appendix A.1 shows that the assumption of proportional hazards appears reasonable in TIOSPIR.*

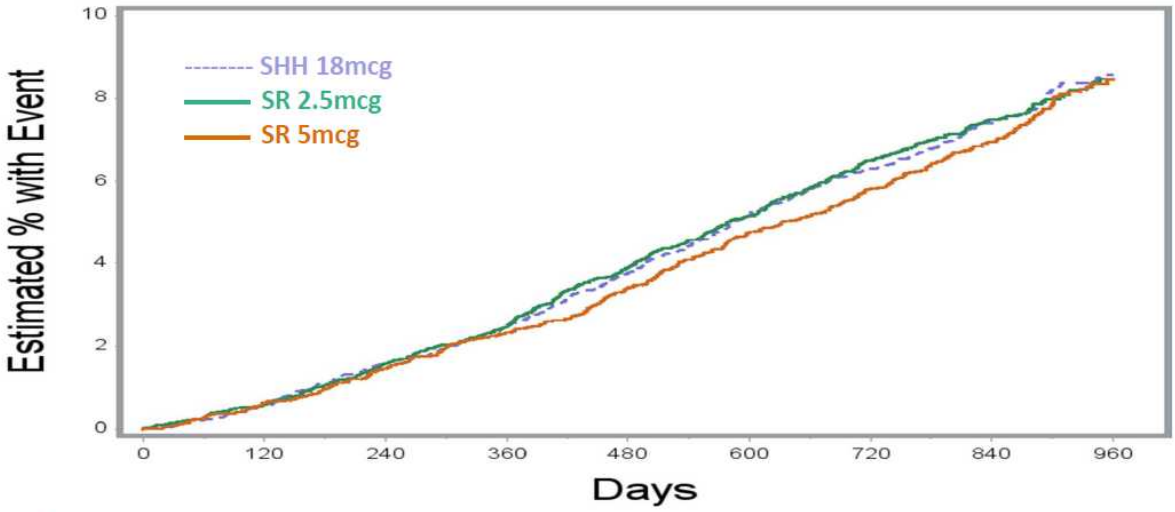
Table 9: Primary/Sensitivity Analysis Results (DAS)

	SHH 18mcg (N = 5694)	**SR 2.5mcg (N = 5730)**	**SR 5mcg (N = 5711)**
On-study Analysis of Death			
Number (%) of **Death**	439 (7.7)	440 (7.7)	423 (7.4)
Incidence Rate per 100 PY	3.4	3.3	3.2
Mean (SD) Days until Death	481.7 (238.3)	470.4 (232.9)	497.8 (245.5)
HR (95% CI) *, vs. SHH 18mcg		**1.00 (0.87, 1.14)**	**0.96 (0.84, 1.09)**
On-treatment Analysis of FAE			
Number (%) of **FAE**	357 (6.3)	359 (6.3)	326 (5.7)
Incidence Rate per 100 PY	3.0	3.0	2.8
Mean (SD) Days until FAE	422.8 (245.0)	413.7 (237.2)	450.6 (254.7)
HR (95% CI) *, vs. SHH 18mcg		**1.00 (0.86, 1.16)**	**0.91 (0.79, 1.06)**
On-treatment Analysis of Death (reviewer)	299 (5.3)	321 (5.6)	284 (5.0)
Number (%) of **Death**	2.5	2.7	2.4
Incidence Rate per 100 PY	460.9 (247.4)	455.9 (238.2)	488.6 (252.5)
Mean (SD) Days until Death		**1.07 (0.91, 1.25)**	**0.95 (0.81, 1.12)**
HR (95% CI) *, vs. SHH 18mcg			

Source: created by reviewer.
*: Cox proportional hazards model with treatment group as the only covariate.

The Kaplan-Meier plot of deaths by treatment is displayed in Figure 3. The survival curves of the three comparison groups are generally similar to the other.

Figure 3: Kaplan-Meier Plot of Time to Death (DAS, on-study)



N At risk:									
SHH 18	5694	5660	5601	5545	5472	5390	5102	3552	532
SR 2.5	5730	5695	5637	5583	5501	5423	5159	3578	546
SR 5	5711	5675	5626	5576	5510	5430	5174	3597	520

Source: Created by reviewer.

3.3.1.4.2 Adjudicated Cause of Death

A total of 1302 subjects in the DAS died during the vital status observation period. As shown in the primary analysis of time to death from any cause, the percentage of deaths was similar in the three tiotropium treatment groups (7.7%, 7.7%, and 7.4% in the SHH 18mcg, SR 2.5mcg, and SR 5mcg groups, respectively). Adjudicated primary cause of death by treatment is summarized in Table 10 based on MedDRA SOC level, by decreasing frequency. The three most common SOCs adjudicated as primary causes of death were respiratory, thoracic and mediastinal disorders (369 subjects, 2.2%); general disorders and administration site conditions (320 subjects, 1.9%); and neoplasms benign, malignant and unspecified (including cysts and polyps) (305 subjects, 1.8%). All other SOCs were adjudicated in a frequency less than 1% in the total population. The frequencies of adjudicated causes of death were comparable across the three treatment groups at the level of SOCs.

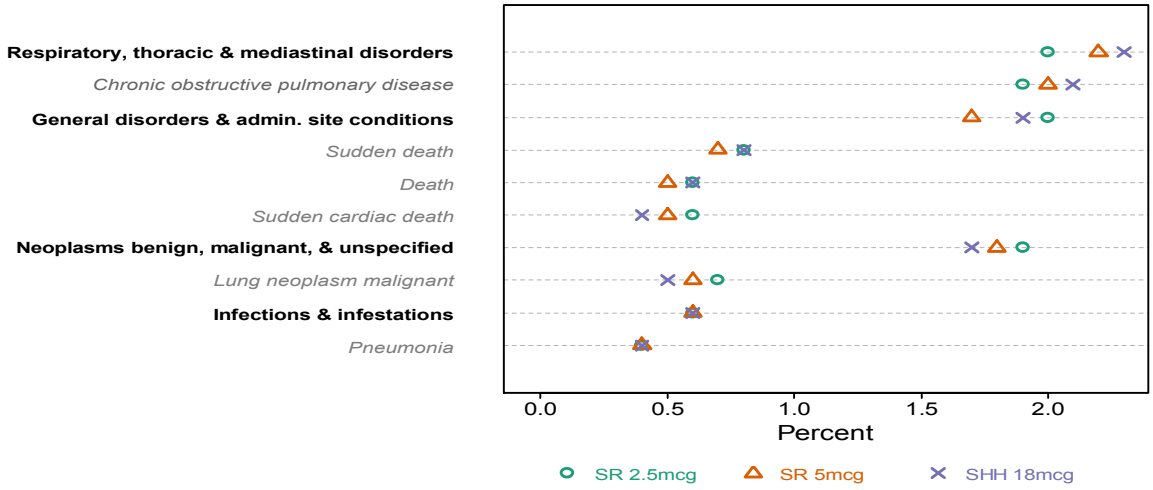
Table 10: Frequency of Adjudicated Primary Cause of Death by Treatment (DAS)

System organ class	Tio R 2.5		Tio R 5		Tio HH 18		Total	
	N	(%)	N	(%)	N	(%)	N	(%)
Number of subjects	5730	(100.0)	5711	(100.0)	5694	(100.0)	17135	(100.0)
Total with primary cause of death determined by adjudication	440	(7.7)	423	(7.4)	439	(7.7)	1302	(7.6)
Respiratory, thoracic and mediastinal disorders	116	(2.0)	123	(2.2)	130	(2.3)	369	(2.2)
General disorders and administration site conditions	117	(2.0)	96	(1.7)	107	(1.9)	320	(1.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	110	(1.9)	100	(1.8)	95	(1.7)	305	(1.8)
Infections and infestations	34	(0.6)	34	(0.6)	34	(0.6)	102	(0.6)
Cardiac disorders	22	(0.4)	27	(0.5)	17	(0.3)	66	(0.4)
Gastrointestinal disorders	6	(0.1)	10	(0.2)	16	(0.3)	32	(0.2)
Injury, poisoning and procedural complications	11	(0.2)	11	(0.2)	16	(0.3)	38	(0.2)
Nervous system disorders	13	(0.2)	16	(0.3)	13	(0.2)	42	(0.2)
Vascular disorders	5	(0.1)	3	(0.1)	5	(0.1)	13	(0.1)
Hepatobiliary disorders	3	(0.1)	1	(0.0)	2	(0.0)	6	(0.0)
Musculoskeletal and connective tissue disorders	1	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Psychiatric disorders	1	(0.0)	2	(0.0)	4	(0.1)	7	(0.0)
Renal and urinary disorders	1	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)

Source: Sponsor's clinical study report. Tio R 2.5 = SR 2.5mcg; Tio R 5 = SR 5mcg; Tio HH 18 = SHH 18mcg.

By MedDRA preferred term, the most frequently adjudicated cause of death was COPD (342 subjects, 2.0%), followed by sudden death (129 subjects, 0.8%), lung neoplasm malignant (105 subjects, 0.6%), death (99 subjects, 0.6%), and sudden cardiac death (88 subjects, 0.5%). The incidence of adjudicated primary cause of death was similar between the three treatment groups for each of these specific event terms, as shown in Figure 4.

Figure 4: Dot Plot of Selective MedDRA Preferred Terms adjudicated as Primary Cause of Death by Treatment (DAS)



Source: Created by reviewer.

As a supplement to the standard MedDRA SOC and PT tables, the applicant collapsed multiple MedDRA preferred terms to single condensed Pharmacovigilance (PV) endpoints as well as SMQs to assess combined occurrence of medically similar primary causes of death of interest. The frequency of subjects with primary cause of death as determined by adjudication (PV endpoint/SMQ) by treatment, user-defined AE category, and preferred term was summarized by the applicant.

Medically similar adjudicated primary causes of death are discussed particularly for two categories of clinical relevance to this trial: respiratory-related disorders and cardiac disorders, including cardiac arrhythmias, ischaemic heart disease, and cardiac failure.

As shown in Table 10, the frequency of adjudicated causes of death categorized within the SOC of respiratory, thoracic, and mediastinal disorders was similar across the three treatment groups (2.3%, 2.0%, and 2.2% in the SHH 18mcg, SR 2.5mcg, and SR 5mcg groups, respectively). The various event terms within respiratory PV endpoint were either balanced across the three treatment groups or infrequent in the total population.

As shown in Table 10, the incidence of death events observed in the cardiac disorders SOC was balanced in the three treatment groups (0.3%, 0.4%, and 0.5% in the SHH 18mcg, SR 2.5mcg, and SR 5mcg groups, respectively). The incidence of adjudicated primary causes of death categorized within the SMQs of cardiac arrhythmias, ischaemic heart disease, cardiac failure, and stroke were evaluated (see Table 11):

- The incidence of SMQ cardiac arrhythmia deaths was comparable: 69 subjects in SHH 18mcg group (1.2%), 84 subjects in SR 2.5mcg group (1.5%), and 70 subjects in SR 5mcg group (1.2%).

- Death events within the SMQ ischaemic heart disease were reported for 30 subjects in the total population: 4 subjects (0.1%) in the SHH 18mcg group, 12 subjects (0.2%) in the SR 2.5mcg group, and 14 subjects (0.2%) in the SR 5mcg group. The incidence rate ratios (IRRs) for SR 5mcg compared to SHH 18mcg is 3.48 (95% CI: 1.15, 10.6). Similar result was observed for SR 2.5mcg compared to SHH 18mcg (IRR is 2.98, 95% CI: 0.96, 9.2). Within the ischaemic heart disease SMQ, death events categorized within the sub-SMQ myocardial infarction (including PTs myocardial infarction, acute myocardial infarction and acute coronary syndrome) were the most frequently reported death events (24 of 30): by treatment, 3 subjects in SHH 18mcg group (0.1%), 10 subjects in SR 2.5mcg group (0.2%), and 11 subjects in SR 5mcg group (0.2%). The incidence rate ratios (IRRs) for SR 5mcg compared to SHH 18mcg is 3.64 (95% CI: 1.02, 13.06). Similar results were observed for SR 2.5mcg compared to SHH 18mcg (IRR is 3.31, 95% CI: 0.91, 12.03).

- Death events categorized within the SMQ cardiac failure (narrow) were reported for 28 subjects (0.2%) in the total population. The incidence of deaths within this SMQ was balanced across the three treatments.

- Death event PTs categorized within the stroke PV endpoint were reported for 35 subjects (0.2%) in the total population. The incidence of all death events within the stroke PV endpoint was balanced in all three treatment groups (0.2% for each).

Table 11: Frequency of Adjudicated Primary Cause of Death (user-defined PV endpoint/SMQ) by Treatment (DAS)

User-defined AE category **Preferred Term**	**SHH 18mcg** **(N = 5694)**	**SR 2.5mcg** **(N = 5730)**	**SR 5mcg** **(N = 5711)**
Number (%) of **Death**	439 (7.7)	440 (7.7)	423 (7.4)
SMQ Cardiac Arrhythmias	69 (1.2)	84 (1.5)	70 (1.2)
SMQ Ischaemic heart disease (IHD) sub-SMQ myocardial infarction (broad) Acute coronary syndrome Acute MI MI **SMQ IHD IRR (95% CI) vs. SHH 18mcg** **sub-SMQ MI IRR (95% CI) vs. SHH 18mcg**	4 (0.1) 3 (0.1) 0 1 2	12 (0.2) 10 (0.2) 0 1 9 **2.98 (0.96, 9.2)** **3.31 (0.91, 12.0)**	14 (0.2) 11 (0.2) 2 3 6 **3.48 (1.15, 10.6)** **3.64 (1.02, 13.1)**
SMQ Cardiac Failure	10 (0.2)	7 (0.1)	11 (0.2)
Stroke PV	11 (0.2)	10 (0.2)	14 (0.2)

Source: Created by reviewer.

3.3.1.4.3 Secondary Endpoints Analysis

As pre-defined, the composite endpoint of MACE includes all fatal events in the two MedDRA SOCs of cardiac and vascular disorders, all protocol-defined outcome events of serious and non-serious MI, stroke, and TIA, and the MedDRA preferred terms sudden death, cardiac death, and sudden cardiac death. Further safety endpoints were time to onset of first stroke, time to onset of first MI and time to onset of first TIA. Table 12 summarizes the number of first occurrence of MACE censored at "on-treatment + 30 days", by treatment group, and the analysis result using the Cox proportional hazards model. In the same table, the analysis results of MACE component are presented at the bottom.

The incidence of MACE is 3.6% in SHH 18mcg group, 3.9% in SR 2.5mcg treatment group, and 3.9% in SR 5mcg group. Based on the HR estimates, the differences observed between either Respimat groups and HandiHaler group were not statistically significant. The results are similar when TIA outcome events are excluded from the composite endpoint MACE. There were no significant differences observed for any of the three MACE components stroke (including non-fatal stroke), MI (including non-fatal MI) and TIA with a HR estimate of MI and TIA numerically favoring the HandiHaler arm compared to either Respimat group. As a MACE

component, cardiovascular (CV) death showed similar incidences across the three arms (1.7% in SHH 18mcg group, 1.8% in SR 2.5mcg treatment group, and 1.7% in SR 5mcg group).

Table 12: Analysis Results of Time to MACE (TS, On-treatment + 30 days)

	SHH 18mcg (N = 5687)	**SR 2.5mcg (N = 5724)**	**SR 5mcg (N = 5705)**
MACE, n (%)	202 (3.6)	224 (3.9)	222 (3.9)
HR (95% CI) ***, vs. SHH 18mcg**		**1.11 (0.91, 1.34)**	**1.10 (0.91, 1.33)**
MACE (No TIA), n (%)	185 (3.3)	201 (3.5)	195 (3.4)
HR (95% CI) ***, vs. SHH 18mcg**		**1.08 (0.89, 1.32)**	**1.05 (0.86, 1.29)**
Stroke, n (%)	57 (1.0)	56 (1.0)	52 (0.9)
HR (95% CI) ***, vs. SHH 18mcg**		**0.98 (0.68, 1.41)**	**0.91 (0.63, 1.33)**
Non-fatal Stroke[1]	49 (0.9)	50 (0.9)	44 (0.8)
HR (95% CI) ***, vs. SHH 18mcg**		**1.01 (0.68, 1.50)**	**0.90 (0.60, 1.35)**
MI, n (%)	52 (0.9)	70 (1.2)	73 (1.3)
HR (95% CI) ***, vs. SHH 18mcg**		**1.34 (0.94, 1.92)**	**1.41 (0.98, 2.00)**
Non-fatal MI[2], n (%)	49 (0.9)	61 (1.1)	64 (1.1)
HR (95% CI) ***, vs. SHH 18mcg**		**1.24 (0.85, 1.80)**	**1.31 (0.90, 1.90)**
TIA, n (%)	20 (0.4)	25 (0.4)	30 (0.5)
HR (95% CI) ***, vs. SHH 18mcg**		**1.24 (0.69, 2.24)**	**1.50 (0.85, 2.65)**
CV Death[3], n (%)	95 (1.7)	102 (1.8)	97 (1.7)
HR (95% CI) ***, vs. SHH 18mcg**		**1.07 (0.81, 1.41)**	**1.02 (0.77, 1.35)**

Source: Created by reviewer.
* Cox proportional hazards model with treatment as the only covariate.
[1] Non−fatal stroke includes all stroke outcome events except those from patients whose primary cause of death was determined by adjudicators to have been stroke.
[2] Non−fatal MI includes all MI outcome events except those from patients whose primary cause of death was determined by adjudicators to have been MI.
[3] Deaths in Cardiac disorders SOC, Vascular disorders SOC and the PTs of cardiac death, sudden death and sudden cardiac death, per adjudication.

The analysis of time to MACE-related deaths included adjudicated fatal MACE events due to MI, stroke, sudden death and other cardiovascular causes (Table 13). The incidence of subjects who experienced death from MACE was 1.8% in SHH 18mcg group, 2.1% in SR 2.5mcg treatment group, 2.0% in SR 5mcg group. The HR estimate was 1.11 (95% CI: 0.85, 1.45) for SR 5mcg versus SHH 18mcg and 1.17 (95% CI: 0.90, 1.53) for SR 2.5mcg versus SHH 18mcg, respectively. The differences observed between treatments were not statistically significant. The HR estimates for time to fatal MI are consistent to the IRR estimates shown in Table 11.

Table 13: Analysis Results of Time to Death due to MACE (DAS, on-study)

	SHH 18mcg (N = 5694)	**SR 2.5mcg (N = 5730)**	**SR 5mcg (N = 5711)**
Death due to MACE[1]			
n (%) of Events	101 (1.8)	119 (2.1)	113 (2.0)
HR (95% CI)*, vs. SHH 18mcg		**1.17 (0.90, 1.53)**	**1.11 (0.85, 1.45)**
Fatal Stroke, n (%)	11 (0.2)	10 (0.2)	14 (0.2)
Fatal MI[2], n (%)	3 (0.1)	10 (0.2)	11 (0.2)
HR (95% CI)*, vs. SHH 18mcg		**3.31 (0.91, 12.0)**	**3.64 (1.02, 13.0)**
Sudden Death[3], n (%)	68 (1.2)	82 (1.4)	67 (1.2)
Other Cardiovascular Cause, n (%)	19 (0.3)	17 (0.3)	21 (0.4)

Source: Created by reviewer.
* Cox proportional hazards model with treatment as the only covariate.
[1] Deaths in Cardiac disorders SOC, Vascular disorders SOC and the PTs of cardiac death, sudden death and sudden cardiac death and in addition deaths in MI SMQ and Stroke PVE. [2] Fatal MI is the same as the sub-SMQ MI (broad) in Table 11. [3] This category includes sudden cardiac death and sudden death.

3.3.2 Placebo-controlled Vital Status Database (VSD)

3.3.2.1 Study Design and Endpoints

3.3.2.1.1 Study Design

Fatal events were collected in the Respimat clinical development program. Four completed randomized trials were utilized to evaluate the association between Respimat 5mcg and all-cause mortality, compared with placebo, in a post-hoc meta- analysis of mortality. This included data from three one-year (48 weeks) Respimat trials (Study 205.254, 205.255 and 205.372) and one 6-month (24 weeks) Study 1205.14.

The four Phase 3 trials included in the placebo-controlled vital status database are all randomized, double-blind, placebo-controlled studies with a parallel group design and enrolled subjects with COPD (see Table 1 in Section 2.1). Data from these four trials were integrated for a meta-analysis of mortality between a pooled Spiriva Respimat 5mcg (SR 5mcg) group and a pooled placebo group.

Reviewer's Comment*: Some of the four randomized controlled trials included doses greater than the SR 5mcg dose. These doses will not be incorporated into the meta-analysis as interest lies in the comparison of SR 5mcg relative to placebo.*

Study 205.254 (02/03/2003 – 06/01/2005) and 205.255 (03/11/2003 – 06/07/2005) were identically-designed, double-blind, placebo controlled, parallel group, multinational studies with a 48-week treatment period. The primary objective of the studies was to compare each of two doses (5 mcg and 10 mcg) of Spiriva Respimat to placebo among subjects with COPD, with respect to bronchodilator efficacy, effect on health status, effect on dyspnoea and effect on frequency of exacerbations. Studies 205.254 and 205.255 randomized 983 and 1007 subjects, respectively. In study 205.254, 319 were assigned placebo, 332 were assigned 5 mcg Spiriva Respimat, and 332 were assigned to 10 mcg titropium Respimat. In study 205.255, 334 were assigned placebo, 338 were assigned 5 mcg Spiriva Respimat, and 335 were assigned to 10 mcg Spiriva Respimat. Subjects who discontinued prematurely from 205.254/255 were included in the retrospective follow-up study 205.392 to collect vital status. In Studies 205.254/255, deaths occurring within 30 days after drug discontinuation should have been notified to the applicant. If a different cause of death was reported in the retrospective follow-up study than in the original studies (205.254 and 205.255), then the original cause of death was used. Study 205.254 and 205.255 were included in the original Respimat NDA submission. In that application, an increased number of deaths were observed in the Respimat treatment groups compared to placebo for 205.254/255, resulting in a Complete Response action for the Spiriva Respimat NDA.

Study 205.372 (10/06/2006 – 01/22/2009) is a randomized, double-blind, placebo-controlled, parallel-group, multicenter and multinational study to assess long term (48-week) efficacy and safety of Tiotropium Inhalation Solution 5 mcg delivered by the Respimat Inhaler in subjects

with COPD. Approximately 4000 subjects were randomly assigned to each of the two treatment groups (SR 5mcg and placebo) in a 1:1 ratio. The two co-primary endpoints for this study were trough FEV1 and time to first COPD exacerbation. As pre-specified in study protocol, the vital status of all prematurely discontinued subjects was collected. The evaluation of mortality was based on the collection of complete data from all subjects, including those who prematurely discontinued, up to the end of the protocol defined treatment period (Day 337).

Study 1205.14 (09/06/2007 – 05/05/2009) is a multinational, randomized, double-blind, placebo- and active-controlled, parallel group efficacy and safety comparison over 24 weeks of three doses (50 mcg, 100 mcg , 200 mcg) of BEA 2180 to tiotropium 5 mcg and placebo delivered by the Respimat inhaler in subjects with COPD. The primary objective of this study was to compare the bronchodilator efficacy of three doses of BEA 2180 inhalation solution delivered by the Respimat inhaler once daily against placebo and tiotropium (5 mcg) for 24 weeks in COPD subjects. Approximately 2000 subjects were randomly assigned to each of the 5 treatment groups in a 1:1:1:1:1 ratio. Per protocol, any patient who discontinued treatment early would be followed on vital status at the time of planned trial completion.

3.3.2.1.2 Endpoints and Adjudication Methods

The endpoint for the post-hoc mortality meta-analysis is time to death from any cause.

A composite endpoint of major adverse cardiovascular events (MACE) is also included in the analysis. The composite endpoint represents fatal events in the MedDRA SOC cardiac disorders and SOC vascular disorders combined with myocardial infarction (fatal and nonfatal), stroke (fatal and non-fatal) and the PTs sudden death, sudden cardiac death and cardiac death. The definition of MACE in the meta-analysis is slightly different from that used in the analysis of TIOSPIR as defined in Section 3.3.1.1.2.

As described in Section 3.3.2.1.1, vital status was followed until the pre-planned end of the 4 trials with fixed-duration, either prospectively or retrospectively. The cause of death was adjudicated by independent experts in the largest trial 205.372. For trials 205.254, 205.255 and 1205.14, the investigator reported cause of death was used in the descriptive analysis.

3.3.2.2 Statistical Methodologies

In this NDA application, the applicant submitted a combined safety database comprised of trials in the clinical development program of Respimat conducted in subjects with COPD. The HandiHaler trials were also included as reference. Four Respimat trials are included in this integrated analysis of mortality for a comparison between Respimat 5 mcg and placebo. There were no documented pre-specified statistical methods associated with the meta-analysis.

3.3.2.2.1 Analysis Methods

3.3.2.2.1.1 Analysis Populations and Event Ascertainment

The evaluation of all-cause mortality in the VSD utilizes an analysis population that is defined as the Treated Set (TS), which consists of all randomized subjects who received at least 1 dose of study drug. All meta-analysis results reported in this review are based on the TS population unless specified otherwise.

For the analysis of time to death from any cause, an "on-study" censoring scheme is utilized for event ascertainment:

- On- study: Events occurred during the course of study, including the active treatment period and the off-treatment follow-up period, were captured. For the three 48-week studies 205.254, 205.255, and 205.372, the data cut-off was set at the end of the planned treatment period (Day 337). For the 24-week study 1205.14, the data cut-off was set at Day 169, which is the end of the pre-planned treatment period.

For the analysis of time to first MACE, an "on- treatment" censoring scheme is utilized for event ascertainment:

- On- treatment + 30 days: Events occurred during the actual course of active treatment plus the following off-treatment period of 30 days were captured.

3.3.2.2.1.2 Time to Death Analysis

All comparative analyses are between the two randomized treatment groups SR 5mcg and placebo. All Respimat arms with a daily dose of 5mcg are combined into one active treatment group, and all the placebo arms are combined into the pooled placebo group.

The primary analysis method for time to death from any cause is a Cox proportional hazards regression model stratified by trial with a fixed effect for treatment to estimate the hazard ratio and corresponding 95% confidence interval of the combined SR 5mcg group versus the combined placebo group.

In this review, as a sensitivity analysis, stratified Mantel-Haenszel (M-H) estimate of the overall incidence rate ratio (IRR) is calculated along with the associated 95% confidence interval using trial as a stratification factor.

A similar stratified Cox proportional hazards model as that used for the analysis of death, was used to calculate the hazard ratio and its corresponding nominal 95% CI comparing Spiriva Respimat 5mcg to placebo with respect to time to onset of first MACE and time to death from MACE, respectively.

Cause of death will be tabulated descriptively using a mixture of adjudicated cause of death when available (Study 205.372) and investigator reported cause of death when adjudication was not conducted (Studies 205.254, 205.255, 1205.14).

3.3.2.2.1.3 MACE Analysis

Time-to-event analysis was performed separately for time to onset of first MACE (on-treatment) and time to death from MACE (on-study).

For these secondary endpoints, similar stratified Cox proportional hazards model, as that used for the analysis of death, was used to calculate the hazard ratio and its corresponding nominal 95% CI comparing Respimat 5mcg to placebo.

3.3.2.3 Subject Disposition, Demographic and Baseline Characteristics

Among all 6170 subjects randomized to either placebo arm or SR 5mcg arm in the 4 trials, a total of 6096[2] (98.8%) subjects received at least 1 dose of study drug were included in the treated set (TS) for the meta-analysis. As shown in Table 14, among the 6096 subjects in the TS population, 3047 (50%) subjects were randomized to receive placebo, while 3049 (50%) subjects were randomized to receive SR 5mcg.

Based upon Table 14, demographic characteristics and baseline risk factors for the 6096 subjects in the 4 trials included in the primary analysis were similar across the treatment groups. In the TS population, there were more male subjects than female subjects (75% versus 25%). Approximately 76% of subjects were White and about 20% were Asian, while 2% of subjects were Black. By region, the highest number of subjects were randomized in the Europe/Africa/Australia/New Zealand region (53.1%), followed by North America (24.3%), Asia (10.1%), and Latin America (2.5%). The mean age was about 65 years. About 19% of subjects were from the U.S. The mean BMI was about 25.6 kg/m^2 at baseline. The mean duration of COPD was 8.4 years. In the treated set, about 63% and 37% of subjects were former and current smoker, respectively, with a mean smoking history of 46.1 pack years.

In the TS population, approximately 12% of subjects had a prior history of cardiac arrhythmias and 14.1% of all subjects had a history of ischaemic heart disease/coronary artery disease at baseline. The incidence of subjects who reported a medical history of MI, stroke or TIA was 3.3%, 5.6%, and 0.8%, respectively. Medical history, including history of cardiovascular and COPD events, was generally similar across the two treatment groups at baseline. Furthermore, the majority of all treated subjects (84.4%) were receiving pulmonary medications at baseline with balanced incidence between the two treatment groups. At baseline, 10.2% of subjects reported concomitant use of inhaled long-acting anticholinergics, 48.5% reported concomitant use of long-acting beta-agonists (LABAs), 53.1% of subjects were taking inhaled short-acting beta adrenergics, and 55.2% of subjects reported concomitant use of inhaled corticosteroids

[2] This excludes data from a questionable site that was reported in Study 205.372.

(ICS). Approximately 40% of all treated subjects were receiving cardiac medications (excluding statins, which were not collected) at baseline. The rate of cardiovascular medication use at baseline was balanced between SR 5mcg arm and placebo arm.

Table 14: Demographics and Baseline Characteristics by Treatment Group (VSD, TS)

	Placebo (N = 3047)	**SR 5mcg (N = 3049)**
Age (yrs), mean±SD	64.8±8.9	64.7±8.9
Sex, % Female	25.4%	24.7%
Race		
White	76.3%	76.6%
Black	1.9%	1.5%
Asian	20.2%	20.3%
Other/Missing	1.6%	1.5%
Region		
North America, US	18.8%	18.9%
North America, non-US	5.5%	5.3%
Latin America	2.6%	2.4%
Euro/Africa/Aus/NZ	52.9%	53.3%
Asia	20.1%	20.1%
BMI (kg/m²), mean±SD	25.6±5.6	25.6±5.5
Current smoker, %	37.3%	37.4%
Smoking history (pk yrs), mean±SD	45.7±25.8	46.4±26.1
Duration of COPD (yrs), mean±SD	8.5±6.8	8.4±6.8
Medical history at baseline (%)		
MI	3.4%	3.2%
Stroke	5.4%	5.7%
Cardiac arrhythmia	10.5%	13.3%
Ischemic heart disease/ CAD	14.4%	13.8%
Use of any respiratory med. (%)	84.2%	84.6%
LABA	47.6%	49.5%
Use of any cardiac med. (%)	40.8%	41.4%

Source: Created by reviewer.

As summarized in Table 15, of all subjects in the treated set, 4987 subjects (81.8%) completed the treatment as planned and 1109 patients (18.2%) discontinued prematurely from the trial medication. In the SR 5mcg group, approximately 84.7% of subjects (2581/3049) had completed active treatment, while 15.3% of subjects (468/3049) had terminated their treatment earlier than planned. The percentage of subjects with premature discontinuation tended to be higher in the combined placebo group (21.0%) than in the SR 5mcg group (15.3%). The most common reason

for premature treatment discontinuation in both groups was due to adverse events. More subjects in the placebo group (187 subjects, 6.1%) than in the SR 5mcg group (81 subjects, 2.7%) discontinued due to worsening of disease under study (COPD). Fewer Subjects in the SR 5mcg group (31 subjects, 1.0%) than in the placebo group (74 subjects, 2.4%) discontinued the study medication due to lack of efficacy. More subjects in the placebo group (89 subjects, 2.9%) than in the SR 5mcg group (45 subjects, 1.5%) refused continuing the study medication.

In general, the trials of 48-week duration have higher drop-out rates compared to the trial with a shorter duration of 24 weeks (Study 1205.14). As presented in Figure 5 the treatment discontinuation rates in the placebo arm are comparable across the three 48-week trials. There is some heterogeneity of early discontinuation in the tiotropium group across the 48-week trials: Study 205.255 has a highest dropout rate of 34.1%, followed by a dropout rate of 28.5% in Study 205.254, then a rate of 18.9% in the largest study (Study 205.372).

Table 15: Subject Disposition in VSD

	Placebo	SR 5mcg	Total
Treated Set (TS)	3047 (100%)	3049 (100%)	6096 (100%)
Completed treatment	2406 (79.0%)	2581 (84.7%)	4987 (81.8%)
Discontinued treatment	641 (21.0%)	468 (15.3%)	1109 (18.2%)
Adverse event	10.2%	7.5%	8.8%
AE study dis. Worse	6.1%	2.7%	4.4%
AE other dis. Worse	0.5%	0.6%	0.5%
AE other	3.6%	4.2%	3.9%
Protocol violation	1.6%	1.9%	1.8%
Lack of efficacy	2.4%	1.0%	1.7%
Refused cont. medic.	2.9%	1.5%	2.2%
Lost to follow-up	1.5%	1.1%	1.3%
Other	2.4%	2.4%	2.4%

Source: Created by reviewer.

Figure 5: Percentage of Subjects with Early Discontinuation by Study and Treatment (VSD)

Source: Created by reviewer.

Table 16 is a high level summary of the extent of exposure by treatment group in the treated set of the placebo-controlled vital status dataset. The total treatment exposure time is 2266 patient years for the placebo group and 2395 patient years for the SR 5mcg group. The discrepancy of exposures between the two groups are due to a higher early treatment discontinuation rate in the combined placebo group (21%), compared to 15% in the combined SR 5mcg group.

Table 16: Extent of Exposure (VSD, TS)

	Placebo	SR 5mcg	Total
Treated Set (TS)	**3047**	**3049**	**6096**
Days on Treatment			
Mean (SD)	271.6 (110.1)	286.9 (95.8)	279.3 (103.5)
Median	336	336	336
Min, Max	1, 455	1, 460	1, 460
Total time on treatment, yrs	2265.6	2395.1	4660.7

Source: Created by reviewer.

As stated in Section 3.3.2.1.1, the subjects who discontinued study medication for any reason were followed up, either prospectively or retrospectively, until the intended duration of each study in order to collect vital status data after treatment discontinuation. The vital status follow up is summarized in Table 17. By Day 337 (or Day 169 for Study 1205.14), vital status was confirmed for 98.5% of all TS subjects. The rates of lost to follow-up are comparable between the two groups.

Table 17: Vital Status Collection (VSD, TS, On-study)

	Placebo (N = 3047)	**SR 5mcg (N = 3049)**	**Total (N = 6096)**
Vital status Confirmed	**2993 (98.2%)**	**3013 (98.8%)**	**6006 (98.5%)**
Alive	2942	2945	5887
Died	51	68	119
Lost to follow-up	**54 (1.8%)**	**36 (1.2%)**	**90 (1.5%)**

Source: Created by reviewer.

3.3.2.4 Results and Conclusions

The first endpoint of the meta-analysis with the VSD is time to death from any cause. Table 18 provides the trial-level detail of all-cause mortality, broken down by treatment groups.

Table 18: Summary of All-cause Mortality by Study and Treatment Group (VSD, TS, On-study)

	Placebo	SR 5mcg	Total
Study 205.254			
N	319	332	651
Number of Events (%), Day 337	7 (2.2)	8 (2.4)	15 (2.3)
Study 205.255			
N	334	338	672
Number of Events (%), Day 337	2 (0.6)	6 (1.8)	8 (1.2)
Study 205.372			
N	1965	1952	3917
Number of Events (%), Day 337	38 (1.9)	52 (2.7)	90 (2.3)
Study 1205.14			
N	429	427	856
Number of Events (%), Day 169	4 (0.9)	2 (0.5)	6 (0.7)

Source: Created by reviewer.

3.3.2.4.1 Time to Death Analysis Results

The primary comparison is between the combined SR 5mcg group and the combined placebo group for the incidence of all-cause mortality during the course of the studies (on-study: including the follow-up period after treatment discontinuation). Below in Table 19, the primary analysis results are presented for all-cause mortality evaluated through a stratified Cox proportional hazards model, along with the sensitivity analysis results including Mantel-Haenszel incidence rate ratio (IRR).

There were 68 (2.2%) deaths observed in the SR 5mcg arm, which corresponds to an incidence rate of 2.6 per 100 patient years, based on a total of 2574 patient years of follow-up in the SR 5mcg arm. There were 51 (1.7%) observed deaths during 2571 patient years of follow-up in the placebo arm, corresponding to an incidence rate of 2.0 per 100 patient years.

Based on the Cox regression model, the estimated hazard ratio of death for SR 5mcg vs. placebo is 1.33 with 95% confidence interval (0.93, 1.92). The presented results were identical between the stratified Cox regression and the Mantel-Haenszel method. While both methods found the incidence of all-cause mortality to be slightly higher in the SR 5mcg group compared to the placebo, the result is not statistically significant with a 95% confidence interval including 1.

Table 19: Mortality Analysis Results (VSD, TS, On-study)

	Placebo (N = 3047)	**SR 5mcg (N = 3049)**
Number (%) of **Death**	51 (1.7)	68 (2.2)
Total Years at Risk	2571	2574
Incidence Rate per 100 PY	2.0	2.6
Mean (SD) Days until Death	165.7 (90.3)	179.2 (90.3)
HR (95% CI) ***,** vs. Placebo		**1.33 (0.93, 1.92)**
M-H IRR (95% CI) †, vs. Placebo		**1.33 (0.93, 1.92)**

Source: Created by reviewer.

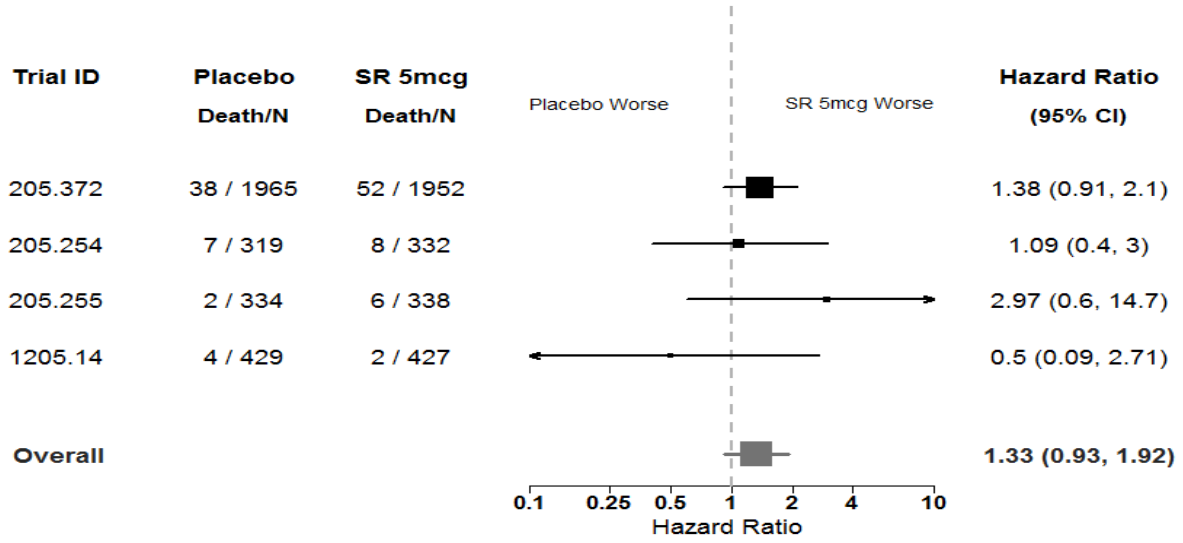
* Cox regression model stratified by study

† Mantel-Haenszel incidence rate ratio, stratified by study.

The forest plot of the hazard ratios of the mortality endpoint (on-study) is presented in Figure 6 for the comparison of SR 5mcg group and placebo group. The individual hazard ratio and the corresponding 95% CI of each trial calculated from a Cox regression model are shown, where the size of the symbol for each hazard ratio corresponds to the number of deaths of the trial. The overall HR and its 95% CI are shown at the bottom.

None of the 4 randomized trials showed a statistically significant difference between SR 5mcg and placebo. For Study 205.372 with the largest size, the individual HR of SR 5mcg compared to placebo was 1.38 with a 95% CI of (0.91, 2.1). The HR estimates vary for other smaller studies and are generally associated with a wide confidence interval due to the small number of deaths observed in these trials.

Figure 6: Forest Plot of Time-to-Event Analysis of Death (VSD, TS, On-study)



Source: Created by reviewer.

3.3.2.4.2 Cause of Death

As shown in the analysis of time to death from any cause, the percentage of deaths was 1.7% in the combined placebo arm and 2.2% in the combined SR 5mcg groups. A total of 119 subjects died during the vital status observation period. The primary cause of death by treatment is summarized in Table 20 based on the MedDRA SOC level. All SOCs were reported or adjudicated in a frequency less than 1% in the total population. The most common SOCs adjudicated or reported as primary causes of death were: general disorders and administration site conditions (34 subjects, 0.6%); respiratory, thoracic and mediastinal disorders (26 subjects, 0.4%); and cardiac disorders (23 subjects, 0.4%), followed by infections and infestations (18 subjects, 0.3%) and neoplasms benign, malignant and unspecified (including cysts and polyps) (13 subjects, 0.2%). All other SOCs were reported even less infrequently. At the level of SOC,

some numerical imbalance exists in cardiac disorders (7 in placebo vs. 16 in SR 5mcg), infections and infestations (12 in placebo vs. 6 in SR 5mcg) and neoplasms benign, malignant and unspecified (including cysts and polyps) (3 in placebo vs. 10 in SR 5mcg). None of the imbalances are conclusive due to the small number of events.

The most frequent MedDRA preferred term reported/adjudicated as cause of death was death (19 subjects), followed by COPD (15 subjects), sudden death (14 subjects) and myocardial infarction (9 subjects). The frequency is lower for other terms.

Table 20: Frequency of Primary Cause of Death by Treatment (VSD, TS, On-study)

SOC	Placebo **(N = 3047)**	SR 5mcg **(N = 3049)**
Cardiac disorders	7	16
Gastrointestinal disorders	3	1
General disorders and administration site conditions	15	19
Infections and infestations	12	6
Injury, poisoning and procedural complications	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	10
Nervous system disorders	2	1
Psychiatric disorders	1	1
Renal and urinary disorders	0	2
Reproductive system and breast disorders	0	1
Respiratory, thoracic and mediastinal disorders	14	12

Source: Created by reviewer.

3.3.2.4.3 MACE Analysis

The post-hoc meta-analysis included time-to-event analyses of a composite endpoint of MACE, which includes all fatal events in the MedDRA SOC cardiac disorders and SOC vascular disorders combined with myocardial infarction (fatal and nonfatal), stroke (fatal and non-fatal) and the PTs sudden death, sudden cardiac death and cardiac death. Table 21 summarizes the number of first occurrence of MACE censored at "on-treatment + 30 days", by the treatment group, and the analysis result using the stratified Cox proportional hazards model. The analysis results of the MACE components, MI, stroke and cardiovascular death are presented at the bottom of the same table. The sub-categories non-fatal stroke and non-fatal MI are presented in the same table with the corresponding incidence rate ratio estimate and its 95% confidence interval, calculated by Mantel-Haenszel method to adjust for trial.

The incidence of MACE is 1.6% in the placebo group and 1.5% in SR 5mcg treatment group. Based on the HR estimates, the differences observed between the two treatments were not statistically significant for this composite endpoint. There was no significant difference observed for either stroke, MI or their non-fatal components with all HR/IRR estimates numerically

favoring the SR 5mcg group. The hazard ratio estimate of cardiovascular death is greater than 1 with a 95% CI including 1.

Table 21: Analysis Results of Time to MACE (VSD, TS, on-treatment + 30 days)

	Placebo (N = 3047)	**SR 5mcg (N = 3049)**
MACE, n (%)	49 (1.6)	46 (1.5)
HR (95% CI)*, vs. Placebo		**0.90 (0.60, 1.34)**
Stroke, n (%)	17 (0.6)	13 (0.4)
HR (95% CI)*, vs. Placebo		**0.73 (0.35, 1.50)**
Non-fatal Stroke[1], n (%)	16 (0.5)	12 (0.4)
IRR (95% CI)†, vs. Placebo		**0.72 (0.34, 1.51)**
MI, n (%)	21 (0.7)	16 (0.5)
HR (95% CI)*, vs. Placebo		**0.73 (0.38, 1.40)**
Non-fatal MI[2], n (%)	18 (0.6)	9 (0.3)
IRR (95% CI)†, vs. Placebo		**0.48 (0.21, 1.05)**
CV Death[3], n (%)	15 (0.5)	26 (0.9)
HR (95% CI)*, vs. Placebo		**1.68 (0.89, 3.17)**

Source: Created by reviewer.
* Cox proportional hazards model stratified by study with treatment group as the only covariate.
† Mantel-Haenszel incidence rate ratio, stratified by study.
[1] SMQ Ischaemic heart disease sub−SMQ Myocardial infarction (broad) (non−fatal).
[2] BI Stroke PVE (non−fatal).
[3] Deaths in cardiac disorder SOC, vascular disorder SOC, stroke PVE, PTs of sudden cardiac death, cardiac death, and sudden death, investigator reported.

The incidence of subjects who experienced death from MACE by adjudication/investigator-reporting was 0.4% in placebo group and 0.8% in SR 5mcg group (Table 22). The HR was 2.00 (95% CI: 1.03, 3.88) for SR 5mcg versus placebo. The numerical imbalance in death due to MACE was primarily driven by the imbalance in fatal MI and sudden death, though both with a small number of events.

Table 22: Analysis Results of Time to Death due to MACE (VSD, TS, on-study)

	Placebo (N = 3047)	**SR 5mcg (N = 3049)**
Death due to MACE		
n (%) of Events	13 (0.4)	26 (0.8)
HR (95% CI)*, vs. Placebo		**2.00 (1.03, 3.88)**
Fatal MI, n (%)	2 (0.1)	9 (0.3)
IRR (95% CI) †, vs. Placebo		**4.49 (0.96, 21.0)**
Fatal Stroke, n (%)	1	1
Sudden Death[1], n (%)	5 (0.2)	9 (0.3)
Other Cardiovascular Cause, n (%)	5 (0.2)	7 (0.2)

Source: Created by reviewer.
* Time to death was analyzed using Cox regression, stratified by study.
† Mantel-Haenszel incidence rate ratio, stratified by study.
[1] This category includes sudden cardiac death and sudden death.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 TIOSPIR

In the following sections, on-study analysis results for all-cause mortality are evaluated for specific subgroups in TIOSPIR. The subgroup analyses include 11,392 subjects (treated set) randomized to either Spiriva HandiHaler 18mcg group (5687 subjects) or Spiriva Respimat 5mcg group (5705 subjects) only since 5mcg daily is the proposed dose submitted in the Respimat NDA. It should be noted that these analyses are exploratory in nature to assess general trends. There were no protocol-defined multiplicity corrections for subgroup analyses and as such results are presented using unadjusted nominal 95% confidence intervals for each of the subgroup analyses. Consistent with the method used in the primary analysis, all hazard ratios were estimated through a Cox proportional hazards model controlling for treatment.

4.1.1 Gender, Age, Race and Geographic Region

Evaluations for gender, age, race and geographic region are presented in the paragraphs that follow. A forest plot combining all results is presented in Figure 7.

4.1.1.1 Gender

Among the 11,392 subjects, 8169 (71.7%) were male and 3223 (28.3%) were female. Among the 860 subjects who died during the study, 647 were reported in male subjects (mortality rate of 7.9%) and 213 were reported in female subjects (mortality rate of 6.6%).

Among male subjects, the risk of mortality appeared slightly lower in the Respimat group than in the HandiHaler group, HR 0.95, 95% CI (0.81, 1.10). Among female subjects, the risk of developing a fatal event was similar between the two groups, HR 0.98, 95% CI (0.75, 1.28).

4.1.1.2 Age

Among the 11,392 subjects, 3179 (27.9%) were younger than 60 years old, 4487 (39.4%) were between 60 and 69 and 3726 (32.7%) were older than 69. Among the 860 subjects who died during the study, 135 deaths were reported in subjects aged younger than 60 years (mortality rate of 4.2%), 298 deaths were reported in subjects aged between 60 and 69 years (mortality rate of 6.6%), while 427 deaths were reported in subjects in the oldest age group (mortality rate of 11.5%).

Among subjects aged younger than 60 years, the risk of all-cause mortality was similar between Respimat and HandiHaler, HR 1.03, 95% CI (0.74, 1.45). Among subjects aged between 60 and 69, the risk was lower in the Respimat group, HR 0.88, 95% CI (0.70, 1.11). For those subjects aged older than 69 years, the risk appeared to be similar between the two treatment groups, HR 0.99, 95% CI (0.82, 1.20).

4.1.1.3 Race

Among the 11,392 treated subjects, 9280 (83.8%) were White, 179 (1.6%) were Black, 1618 (14.6%) were Asian, and 315 subjects have their race information missing. Among the 860 subjects with fatal events, 702 were reported in White subjects (mortality rate of 7.6%), 16 were reported in Black subjects (mortality rate of 8.9%), 121 were reported in Asian subjects (mortality rate of 7.5%), and 21 were reported in a subject with unknown race (mortality rate of 6.7%).

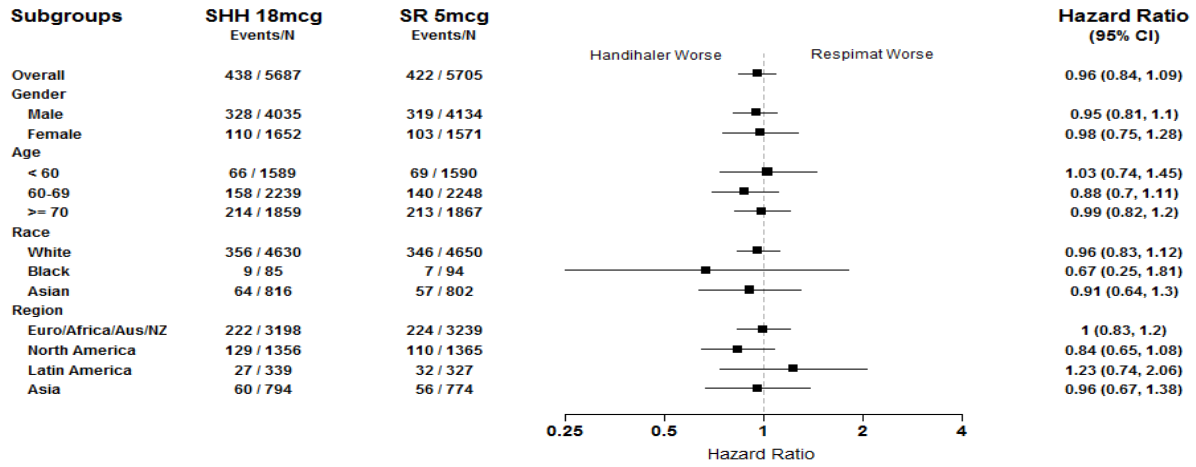
Among White subjects, the risk of all-cause mortality was slightly lower in the Respimat group than in the comparator group, HR 0.96, 95% CI (0.83, 1.12). Among Black subjects, the risk was lower in the Respimat arm than in the HandiHaler arm, along with a relatively wide confidence interval due to the small number of deaths in this race group, HR 0.67, 95% CI (0.25, 1.81). Among Asian subjects, the risk appeared to be slightly lower in the Respimat group than in the comparator group, HR 0.91, 95% CI (0.64, 1.30).

4.1.1.4 Region

Among the 11,392 subjects, 2721 (23.9%) were randomized in North America, 6437 (56.5%) were randomized in Europe/Africa/Australia/New Zealand, 1568 (13.8%) were randomized in Asia, and 666 (5.8%) were randomized in Latin America. Among the 860 subjects who died before the study end, 239 deaths were reported in North America (mortality rate of 8.8%), while 446 deaths were reported in Europe/Africa/Australia/New Zealand (mortality rate of 6.9%), 116 deaths were reported in Asia (mortality rate of 7.4%), and 59 deaths were reported in Latin America (mortality rate of 8.9%).

The HR estimate for North America subjects was lower than 1, HR 0.84, 95% CI (0.65, 1.08), as well as for Asia, HR 0.96, 95% CI (0.67, 1.38). Among Latin America subjects, the effect trended to the opposite direction, HR 1.23, 95% CI (0.74, 2.06) with a small number of deaths. For the rest of the world (Europe/Africa/Australia/New Zealand), the risk of mortality is about the same between Respimat and HandiHaler, HR 1.00, 95% CI (0.83, 1.20).

Figure 7: Forest Plot of Hazard Ratio of Mortality by Baseline Demographics (TS, On-study)



Source: Created by reviewer.

4.1.2 Baseline Risk Factors

To determine if the health history of the subjects had any impact on mortality risk, the baseline BMI, smoking history, baseline myocardial infarction and baseline cardiac arrhythmia were evaluated. A forest plot combining all these subgroup analysis results is presented in Figure 8.

4.1.2.1 BMI

Among the 11,392 subjects, 733 (6.4%) had baseline BMI < 18.5 kg/m^2, 4398 (38.6%) had baseline BMI between 18.5 and 25 kg/m^2, 3748 (32.9%) had baseline BMI between 25 and 30 kg/m^2, while 2513 subjects (22.1%) had BMI >= 30 kg/m^2 at baseline. Among the 860 subjects with fatal events, 127 were reported in subjects of the lowest BMI category (mortality rate of 17.3%), 360 were reported in the subjects with BMI between 18.5 and 25 kg/m^2 (mortality rate of 8.2%), 214 were reported in the subjects with BMI between 25 and 30 kg/m^2 (mortality rate of 5.7%), and 159 were reported in the highest BMI category (mortality rate of 6.3%).

Among the subjects with BMI < 18.5 kg/m^2, the risk of mortality is comparable between Respimat and HandiHaler, HR 0.98, 95% CI (0.69, 1.38). For the two BMI categories sitting in the middle, the risk of mortality is slightly lower in the Respimat group than in the HandiHaler group [BMI 18.5 – 25 kg/m^2: HR 0.93, 95% CI (0.76, 1.15); BMI 25 – 30 kg/m^2: HR 0.88, 95% CI (0.67, 1.15)]. In contrast, among the subjects with the highest BMI (>= 30 kg/m^2), the risk of mortality is higher in the Respimat arm than in the HandiHaler arm, HR 1.14, 95% CI (0.84, 1.56).

4.1.2.2 Smoking Status

Among the 11,392 subjects, 7038 (61.8%) were classified as an “ex- smoker” at baseline and 4352 (38.2%) were considered as “current smoker” at baseline, while 2 subjects were classified

as “never smoked”. Among the 860 subjects with the primary events, 567 deaths were reported among former smokers (mortality rate of 8.1%), while 293 deaths were reported from current smokers (mortality rate of 6.7%).

Both subgroups had a HR estimate close to 1 [ex- smoker: HR 0.93, 95% CI (0.79, 1.09); current smoker: HR 1.03, 95% CI (0.82, 1.29)].

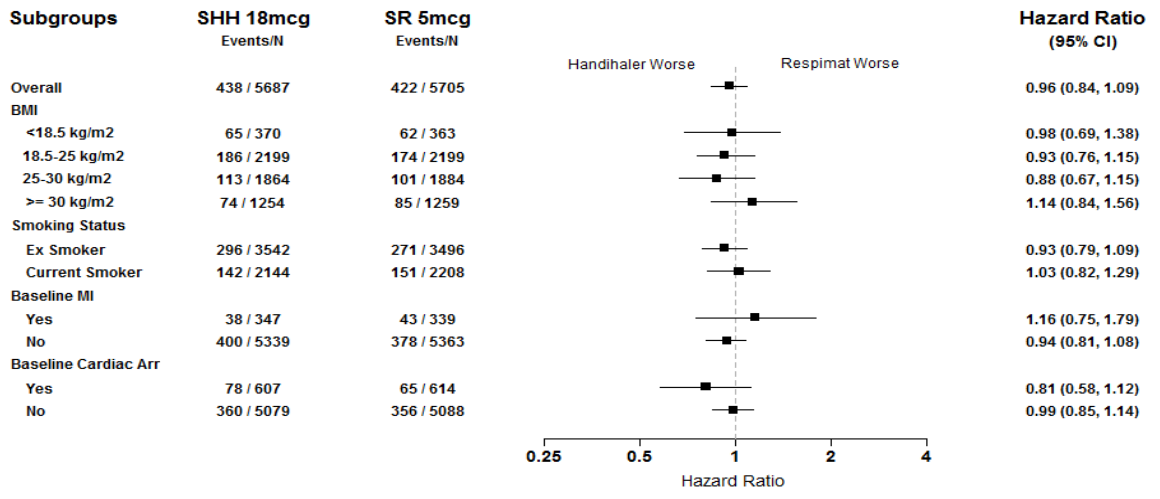
4.1.2.3 Prior Myocardial Infarction

Among the 11,392 subjects, 686 (6%) had a history of myocardial infarction. Among those subjects with prior MI, 81 died during the course of the trial (mortality rate of 11.8%). Based on the time-to-event analysis of death, it was found that the two subgroups (with prior MI and no prior MI) both had a HR point estimate close to 1, while the subjects with MI history had a slightly higher risk in the Respimat group compared to the group with the HandiHaler device, HR 1.16, 95% CI (0.75, 1.79). For those who didn’t have prior MI, the HR is slightly lower than 1, HR 0.94, 95% CI (0.81, 1.08).

4.1.2.4 Prior Cardiac Arrhythmia

Among the 11,392 subjects, 1221 (10.7%) had a history of cardiac arrhythmia. Among those subjects with prior cardiac arrhythmia, 143 deaths were reported during the course of the trial (mortality rate of 11.7%), with a lower mortality risk observed in the Respimat group compared to the HandiHaler group, HR 0.81, 95% CI (0.58, 1.12). For those who didn’t have a history of cardiac arrhythmia, the HR was 0.99, with a 95% CI (0.85, 1.14).

Figure 8: Forest Plot of Hazard Ratio of Mortality by Baseline Risk Factors (TS, On-study)



Source: Created by reviewer.

4.2 Vital Status Database (VSD)

In the following sections, on-study analysis results for all-cause mortality are presented for specific subgroups in the combined vital status database. The subgroup analyses utilize the treated set comprised of 3047 subjects randomized to the placebo group and 3049 subjects randomized to the Respimat 5mcg group. It should be noted that these analyses are exploratory in nature to assess general trends. There were no protocol-defined multiplicity corrections for subgroup analyses and as such results are presented using unadjusted nominal 95% confidence intervals for each of the subgroup analyses. Consistent with the method used in the mortality analysis of the VSD, all hazard ratios were estimated through a Cox proportional hazards model stratified by trial and controlling for treatment.

4.2.1 Gender, Age and Race

Evaluations for gender, age and race are presented in the paragraphs that follow. A forest plot combining all results is presented in Figure 9.

4.2.1.1 Gender

Among the 6096 subjects in the treated set, 4570 (75%) were male and 1526 (25%) were female. Among the 119 subjects who died during the study, 97 were reported in male subjects (mortality rate of 2.1%) and 22 were reported in female subjects (mortality rate of 1.4%).

In both male and female subjects, the risk of mortality appeared higher in the Respimat group than in the placebo group [Male: HR 1.31, 95% CI (0.87, 1.95); Female: HR 1.46, 95% CI (0.62, 3.42)].

4.2.1.2 Age

Among the 6096 treated subjects, 1693 (27.8%) were younger than 60 years old, 2513 (41.2%) were between 60 and 69 and 1890 (31%) were older than 69. Among the 119 subjects who died during the studies, 17 deaths were reported in subjects aged younger than 60 years (mortality rate of 1.0%), 48 deaths were reported in subjects aged between 60 and 69 years (mortality rate of 1.9%), while 54 deaths were reported in subjects in the oldest age group (mortality rate of 2.9%).

Among subjects aged younger than 60 years, the risk of all-cause mortality was higher in the Respimat arm than in placebo arm, HR 1.45, 95% CI (0.55, 3.82). Among subjects aged between 60 and 69, the risk was slightly higher in the Respimat group, HR 1.15, 95% CI (0.65, 2.04). For those subjects aged older than 69, the risk appeared to be higher in the Respimat arm than in placebo arm, HR 1.47, 95% CI (0.86, 2.54).

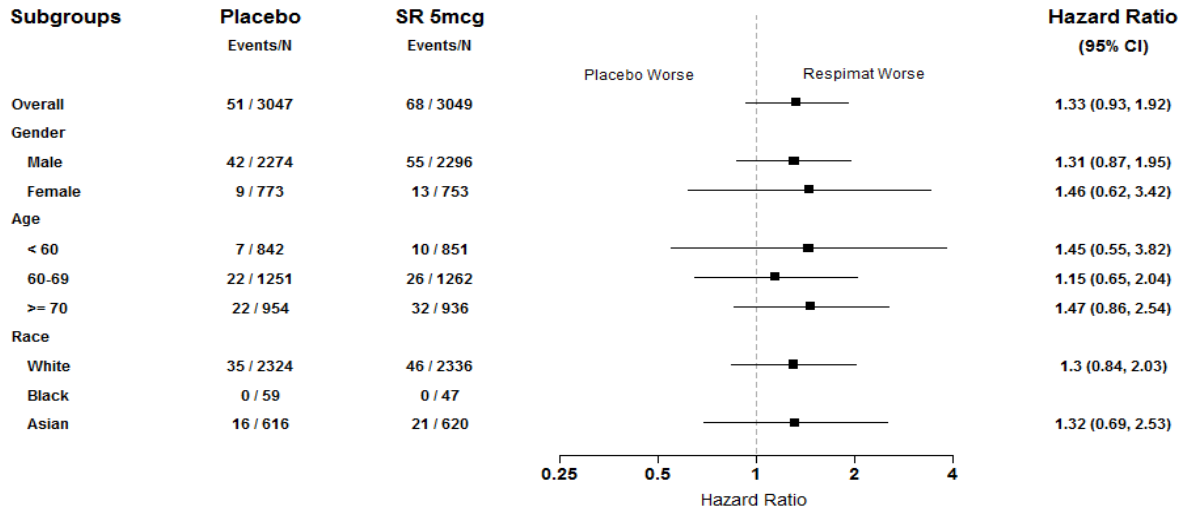
4.2.1.3 Race

Among the 6096 subjects, 4660 (77.6%) were White, 106 (1.8%) were Black, 1236 (20.6%) were Asian, and 94 subjects had their race information as missing or “other”. Among the 119

subjects with fatal events, 81 were reported in White subjects (mortality rate of 1.7%), 37 were reported in Asian subjects (mortality rate of 3.0%), while no death was reported in Black subjects.

Among White subjects, the risk of all-cause mortality was higher in the Respimat group than in the comparator group, HR 1.30, 95% CI (0.84, 2.03). Similar effect was observed among Asian subjects, HR 1.32, 95% CI (0.69, 2.53).

Figure 9: Forest Plot of Hazard Ratio of Mortality by Baseline Demographics (VSD, TS, On-study)



Source: Created by reviewer.

4.2.2 Baseline Risk Factors

To determine if the health history of the subjects had any impact on mortality risk in the VSD, the baseline BMI, history of myocardial infarction and cardiac arrhythmia were evaluated. A forest plot combining all these subgroup analysis results is presented in Figure 10.

4.2.2.1 BMI

Among the 6096 subjects, 453 (7.4%) had baseline BMI < 18.5 kg/m^2, 2581 (42.5%) had baseline BMI between 18.5 and 25 kg/m^2, 1920 (31.6%) had baseline BMI between 25 and 30 kg/m^2, while 1126 subjects (18.5%) had BMI >= 30 kg/m^2. Among the 119 subjects with fatal events, 25 were reported in subjects from the lowest BMI category (mortality rate of 5.5%), 48 were reported in the subjects with BMI between 18.5 and 25 kg/m^2 (mortality rate of 1.9%), 28 were reported in the subjects with BMI between 25 and 30 kg/m^2 (mortality rate of 1.5%), and 18 were reported in the highest BMI category (mortality rate of 1.6%).

Among the subjects with BMI < 18.5 kg/m^2, the risk of mortality is slightly lower in the Respimat group than in the placebo group, HR 0.82, 95% CI (0.37, 1.81). For the other three BMI categories, the risk of mortality is higher in the Respimat group than in the comparison

group [BMI 18.5 – 25 kg/m^2: HR 1.49, 95% CI (0.84, 2.66); BMI 25 – 30 kg/m^2: HR 1.43, 95% CI (0.68, 3.03); BMI >= 30 kg/m^2: HR 1.92, 95% CI (0.72, 5.12)].

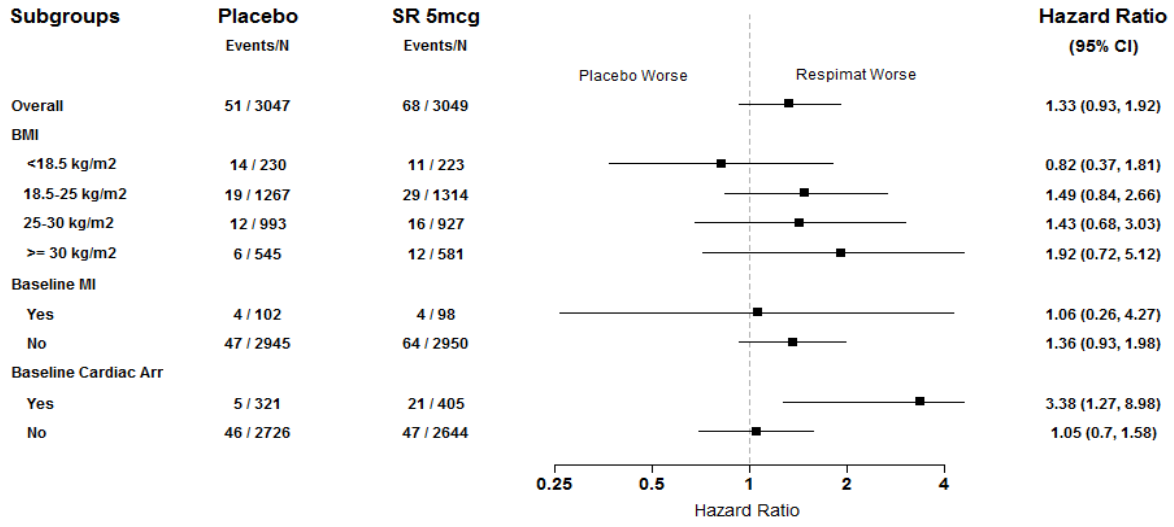
4.2.2.2 Prior Myocardial Infarction

Among the 6096 subjects in the treated set, 200 (3.3%) had a history of myocardial infarction. Among those subjects with prior MI, 8 died during the course of the trials (mortality rate of 4.0%). Among the subjects with MI history, the risk of mortality was similar between the two groups, HR 1.06, 95% CI (0.26, 4.27). For those who didn't have prior MI, the mortality risk is slightly higher in the Respimat group compared to the placebo group, HR 1.36, 95% CI (0.93, 1.98).

4.2.2.3 Prior Cardiac Arrhythmia

Among the 6096 subjects, 726 (11.9%) had a history of cardiac arrhythmia. Among those subjects with prior cardiac arrhythmia, 26 deaths were observed during the course of the trials (mortality rate of 3.6%), with 5 reported in the placebo group and 21 reported in the Respimat group. This resulted in a HR estimate of 3.38 with a 95% CI (1.27, 8.98). For those who didn't have a history of cardiac arrhythmia, the HR is 1.05, with a 95% CI (0.70, 1.58).

Figure 10: Forest Plot of Hazard Ratio of Mortality by Baseline Risk Factors (VSD, TS, On-study)



Source: Created by reviewer.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

5.1.1. TIOSPIR

TIOSPIR is a large-scale safety study designed and powered to rule out a relative excess mortality risk of 25% for Spiriva Respimat vs. Spiriva HandiHaler. It provides a total of 34,085 patient years of treatment exposure to Spiriva which includes 11,343 patient years of exposure to the proposed dose of Respimat 5 mcg. Of the 17,135 randomized subjects, 99.7% had vital status confirmed until the end of this event-driven trial. The pre-specified primary analysis was based upon a Cox proportional hazards model utilizing an "on-study" censoring strategy for the primary endpoint of time to death from any cause. The results of the primary analysis shows no evidence of excess risk of all-cause mortality associated with use of the Respimat device for either dose (2.5mcg and 5mcg) compared to the HandiHaler device and successfully ruled out the pre-defined risk margin of 1.25. Results of sensitivity analyses were consistent with that of the primary analysis of mortality. The frequencies of adjudicated causes of death were comparable across the treatment groups at the MedDRA SOC level.

There was no statistically significant difference observed for the MACE endpoint, or for any of its three components: stroke, MI and TIA. There were no significant imbalances observed for deaths caused by MACE events. Numerical imbalance exists for the subcategory fatal MI, with small number of observed events (3 subjects in HandiHaler group, 10 subjects in Respimat 2.5 mcg group, and 11 subjects in Respimat 5 mcg group). In addition, there was no protocol-defined multiplicity adjustment for the analyses of the subcategory of cardiovascular death. When overall mortality is balanced across comparison arms, caution is warranted in interpreting cause-specific mortality because of competing risk of mortality. Without plausible biological mechanism, such findings should be interpreted carefully.

5.1.2. Vital Status Database (VSD)

In the placebo-controlled vital status database (VSD) comprised of four trials with relatively short duration of either 48 weeks or 24 weeks, vital status information was collected either retrospectively or prospectively. At the end of the fixed duration of these studies, vital status was confirmed for 98.5% of all treated subjects randomized to either the SR 5mcg group (2395 patient years of exposure) or the placebo group (2266 patient years of exposure) . A post-hoc meta-analysis of all-cause mortality was conducted using the mortality data collected in the VSD to evaluate the association of death with the use of Respimat at a daily dose of 5mcg compared to placebo. The analysis using a stratified Cox regression model found the incidence of all-cause mortality to be higher in the SR 5mcg group compared to the placebo group. The result is not statistically significant [HR (95% CI): 1.33 (0.92 – 1.90)]. Causes of deaths at the MedDRA SOC level were all reported or adjudicated in a frequency less than 1% of the total VSD population.

The incidences of MACE are comparable between the combined Respimat 5mcg group and the combined placebo group. There was no significant difference observed for either stroke, MI or their non-fatal components with all HR/IRR estimates numerically favoring the SR 5mcg group. The analysis of time to death caused by MACE showed a HR estimate of 2.00 (95% CI: 1.03, 3.88) for SR 5mcg versus placebo, driven primarily by the numerical imbalance in fatal MI and sudden death. However, no conclusion could be drawn due to the small number of events (fatal MI: 2 subjects in placebo group vs. 9 subjects in Respimat 5 mcg group; sudden death: 5 subjects in placebo group vs. 9 subjects in Respimat 5 mcg group). Based on similar reasons as stated in Section 5.1.1, these imbalances found in such cause-specific mortality sub-categories should be interpreted with caution, while total MACE does not show an increased incidence associated with Respimat 5 mcg use.

5.2 Collective Evidence

5.2.1. UPLIFT

On November 14, 2008, the applicant submitted a 4-year, randomized, placebo-controlled, parallel group study UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium, Study 205.235). UPLIFT randomized nearly 6000 subjects with moderate to severe COPD to either a Spiriva HandiHaler 18 mcg (SHH 18mcg) group or a placebo group. UPLIFT was designed to assess the effects of Spiriva HandiHaler on the rate of decline of lung function in patients with COPD. While primarily an efficacy study, UPLIFT also provided a substantial amount of controlled long-term safety data for Spiriva HandiHaler. In this study, data on deaths, including the vital status of subjects who withdrew from the study, were collected prospectively, and the cause of death was adjudicated in a blinded fashion by an independent committee. By the planned end of the study at Day 1440, vital status was confirmed for 95% of all randomized subjects (Table 23).

Table 23: Vital Status Collection by Day 1440 (UPLIFT)

	Placebo (N = 3006)	**SHH 18mcg (N = 2986)**	**Total (N = 5992)**
Vital status Confirmed	**2842 (94.5%)**	**2849 (95.4%)**	**5691 (95.0%)**
Alive	2351	2419	4770
Died	491	430	921
Lost to follow-up	**164 (5.5%)**	**137 (4.6%)**	**301 (5.0%)**

Source: Created by reviewer.

Utilizing various cut-off days and censoring schemes, the analysis results consistently show a mortality benefit for tiotropium HandiHaler vs. placebo with a hazard ratio estimate less than one, along with an upper bound of 95% CI around 1 (Table 24).

Table 24: Analysis Results of All-cause Mortality (UPLIFT)

	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

Source: Clinical Review of UPLIFT, Table 10, page 43.

Other than overall death, UPLIFT did not show an increase in stroke, MI or cardiovascular death in the tiotropium HandiHaler group compared to placebo, as presented in Table 25. The data on cardiovascular risk and mortality from UPLIFT was thoroughly discussed in a FDA meeting of the Pulmonary–Allergy Drugs Advisory Committee (PADAC) on November 19, 2009. The AC panel voted that the UPLIFT study adequately addressed the potential safety signal of stroke and cardiovascular events. Based upon the input from the PADAC and FDA review of UPLIFT, the Agency concluded that UPLIFT showed that there was no significant increase in stroke, MI, or CV death with Spiriva HandiHaler.

Table 25: Selected Endpoints in UPLIFT

	Spiriva HandiHaler N=3006	Placebo N=2986	Rate Ratio (95% CI)
Fatal Events – adjudicated, Vital Status (Day 1470) dataset			
Mortality – all cause	446 (14.9)	495 (16.5)	0.89 (0.79, 1.01)
COPD Exacerbation – fatal	120 (4.0)	150 (5.0)	0.79 (0.62, 1.01)
Cardiac disorders – fatal	26 (0.9)	32 (1.1)	0.81 (0.48, 1.36)
Myocardial infarction – fatal	11 (0.4)	11 (0.4)	1.00 (0.43, 2.30)
Stroke (CVA) – fatal	14 (0.5)	17 (0.6)	0.82 (0.40, 1.66)
Serious adverse events, on treatment+30 days dataset			
Serious Adverse Events	1540 (51.6)	1509 (50.2)	0.95 (0.88, 1.02)
Cardiac Disorder SAEs	322 (10.8)	350 (11.6)	0.84 (0.73, 0.98)
Myocardial Infarction SAEs	65 (2.2)	84 (2.8)	0.71 (0.52, 0.99)
Stroke SAEs	28 (0.9)	28 (0.9)	0.92 (0.55, 1.56)
Source: NDA 21395, CSR 0205-0235-01-15 (Study 235), pages 735-761, 1031-1035;			

Source: Sponsor's clinical study report of UPLIFT.

5.2.2. Totality of Evidence

TIOSPIR and the four efficacy trials included in the VSD enrolled a typical population of COPD patients which is comparable to the population of subjects enrolled in UPLIFT. All trials obtained vital status information for a high proportion of randomized subjects. The largest number of deaths were observed in the longest trial UPLIFT (921), followed by the largest trial

TIOSPIR (862). The VSD contributes the smallest amount of information in terms of total treatment exposure, vital status observation years and total observed deaths (Table 26).

Inconsistent findings of mortality were observed across the three data sources. An excess risk of all-cause mortality was not observed in TIOSPIR (Respimat vs. HandiHaler) nor in UPLIFT (HandiHaler vs. Placebo). However, in the post-hoc meta-analysis of the VSD, the incidence of all-cause mortality is higher in the Respimat 5mcg group compared to the placebo, though not statistically significant.

Table 26: Summary of Mortality Data from UPLIFT, TIOSPIR and the VSD

	UPLIFT		TIOSPIR		Vital Status Database	
Treatment	**Placebo**	**SHH 18mcg**	**SHH 18mcg**	**SR 5mcg**	**Placebo**	**SR 5mcg**
N	3006	2986	5694	5711	3047	3049
Total V/S F/U, yrs	10872	10927	13050	13135	2571	2574
Deaths	491	430	439	423	51	68
IR per 100 PYs	4.5	3.9	3.4	3.2	2.0	2.6
HR (95% CI)		**0.87 (0.76, 0.99)**		**0.96 (0.84, 1.09)**		**1.33 (0.93, 1.92)**

Source: Created by reviewer.

Comparing the incidence rates of all-cause mortality by every 48-week interval among UPLIFT, TIOSPIR and the VSD, the incidence rate of death in the placebo arm of the VSD is 2.0 per 100 patient years, which is lower than any other arms in all three data sources for 0-48 weeks (around 2.4 – 2.6 per 100 patient years), and is the lowest across all the time intervals (Table 27). One possibility is that the increased mortality risk in the Respimat 5mcg arm is due to the unusually low event rate observed in the placebo arm in the VSD.

Table 27: Deaths and Incidence Rates by Interval (UPLIFT, TIOSPIR and the VSD)

	UPLIFT		TIOSPIR		VSD	
Weeks	**SHH 18**	**Placebo**	**SHH 18**	**SR 5**	**SR 5**	**Placebo**
0-48	**64 (2.4)**	**70 (2.6)**	**129 (2.5)**	**125 (2.4)**	**68 (2.6)**	**51 (2.0)**
48-96	93 (3.5)	104 (4.0)	209 (4.2)	175 (3.5)		
96-144	115 (4.6)	121 (4.8)	100 (3.5)	123 (4.3)		
144-192	119 (5.0)	151 (6.4)				

Source: Created by reviewer.

As an exploratory analysis, a network meta-analysis was conducted to integrate all mortality data collected in UPLIFT, TIOSPIR and the four trials included in the VSD for a comparison of Respimat 5 mcg vs. placebo (results shown in Appendix 2, along with the comparison of

HandiHaler vs. placebo). Note that the trials have various duration - a network meta-analysis on the data truncated at 1 year (Day 337) was also conducted, with the results shown at the bottom in the same forest plot. None of the results shows a statistically significant finding. An interesting finding is that the effect of Respimat and HandiHaler are trending in the same direction, whether the full duration of the data or the truncated data are considered. For the one-year data, again, the low mortality incidence observed in the placebo arm of the VSD trials drives the effect to the other direction, for both Respimat and HandiHaler, with no statistical significance suggesting there is not an increased mortality risk of Respimat 5 mcg compared to placebo.

In the VSD, an imbalance was observed for cardiovascular death (death due to MACE) in the Spiriva Respimat group relative to the placebo group (26 vs. 13). Fatal myocardial infarction (9 vs. 2) (and sudden death, 9 vs. 5) is a primary contributor to the observed imbalance. At the same time, TIOSPIR also show an imbalance in fatal MI for Respimat 5mcg vs. HandiHaler 18mcg (11 vs. 3). However, with the small number of events and lack of consistent signal in overall mortality and total MACE (Table 28), it is hard to interpret such an observation.

Table 28: Analysis Results for Mortality, Total MACE and Fatal MI (UPLIFT, TIOSPIR and the VSD)

	UPLIFT **SHH vs. Placebo**	**TIOSPIR** **SR 5mcg vs. SHH**	**Vital status database** **SR 5mcg vs. Placebo**
Mortality (HR)	0.87 (0.76, 0.99)	0.96 (0.84, 1.09)	1.33 (0.93, 1.92)
Total MACE (IRR)	0.80 (0.67, 0.96)	1.10 (0.91, 1.33)	0.90 (0.6, 1.34)
Fatal MI (IRR)	0.78 (0.35, 1.72)	3.64 (1.02, 13.06)	4.49 (0.96, 20.96)

Source: Created by reviewer.

5.2.3 Conclusions and Recommendations

TIOSPIR was designed and powered to evaluate the risk of all-cause mortality associated with the use of the Spiriva Respimat inhalation device, compared to the marketed Spiriva HandiHaler device. TIOSPIR randomized 17,183 subjects and followed up more than 99% of them for the full study duration of this event-driven trial to collect the vital status data. Overall, the data showed no evidence of increased risk of mortality associated with the use of the Respimat for both doses of 2.5 mcg daily and 5 mcg daily, compared to HandiHaler 18 mcg daily.

Based on the primary analysis using the “on-study” censoring scheme, the incidence of all-cause mortality was about the same in the Respimat groups relative to the HandiHaler group. Compared to the active control group, the estimated hazard ratio of Respimat 5 mcg vs. HandiHaler is 0.96 with a 95% CI of (0.84, 1.09), which ruled out a 25% relative increase of

overall death. While various event and event ascertainment resulted in different numerical values of the effect estimates, conclusions are consistent with the primary finding.

While the integrated placebo-controlled vital status database showed an inconsistent but not statistically significant risk increase of mortality in the Spiriva Respimat 5 mcg arm, compared with placebo, the amount of information provided in this database is relatively small compared to UPLIFT and TIOSPIR. It is possible that the elevated mortality risk is a chance finding due to an unusually low incidence rate of death observed in the pooled placebo arm of the vital status database.

Combining the mortality results obtained in another large-scale, long-term, well designed and conducted study UPLIFT, the data is convincing in demonstrating comparable mortality of Spiriva Respimat 5mcg daily to Spiriva HandiHaler 18 mcg daily, as well as to placebo.

There are lingering signals about fatal myocardial infarction in the VSD and TIOSPIR. The small number of events makes it hard to interpret such findings, especially when overall mortality is reassuring and there are no signals with overall MACE.

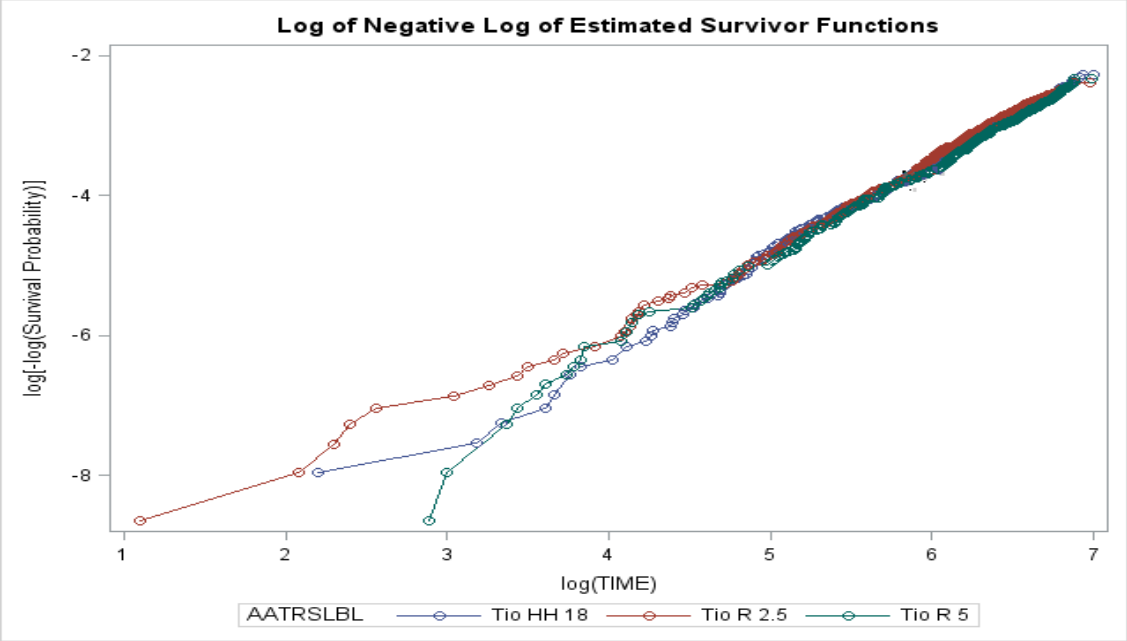
Overall, this NDA resubmission resolved the safety concerns listed in the Complete Response Letter issued on September 16, 2008. The data showed no evidence of increased risk of all-cause mortality associated with the use of Spiriva Respimat compared to Spiriva HandiHaler, for which the safety profile was well-established through a large-scale and long-term study UPLIFT. A drug approval is recommended for Spiriva Respimat 5 mcg once daily based on the data included in the NDA resubmission, from a statistical perspective.

Appendix

A.1 Assessment of Proportional Hazards in Primary Mortality Analysis in TIOSPIR

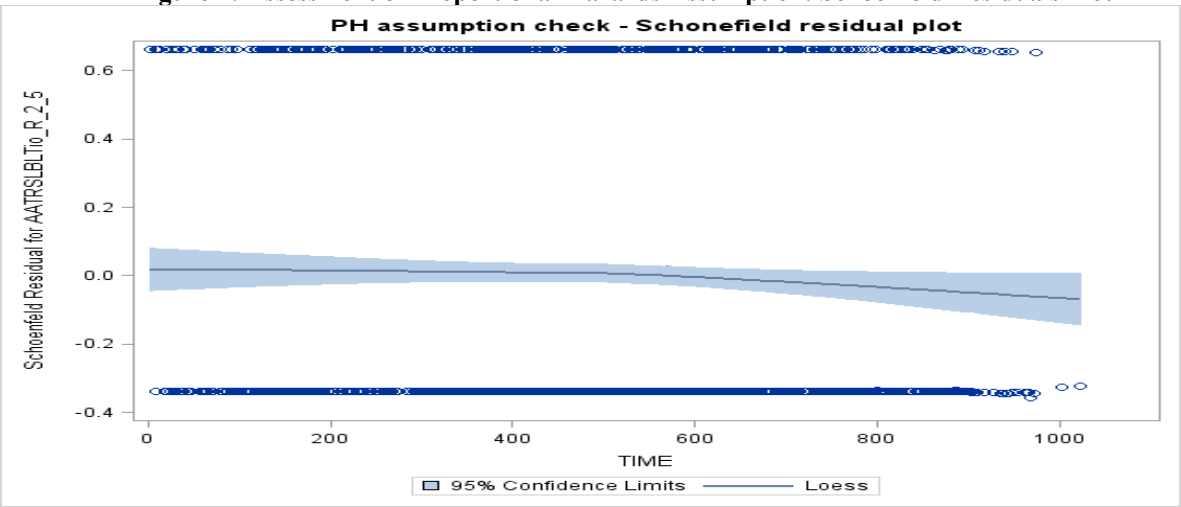
To ensure that the Cox proportional hazards model was justified, the proportional hazards assumption was evaluated by investigating the plots of the log-log survival curve and the Schoenfeld residuals of the data with regards to the primary safety endpoint – all-cause mortality. Both plots (Figure 1 and Figure 2) show that the proportional hazards assumption does hold for the data as the log-log curves for the three treatment groups are generally parallel to each other and the smooth curve resulting from the plotting of the Schoenfeld residuals does approximately lie on y=0.

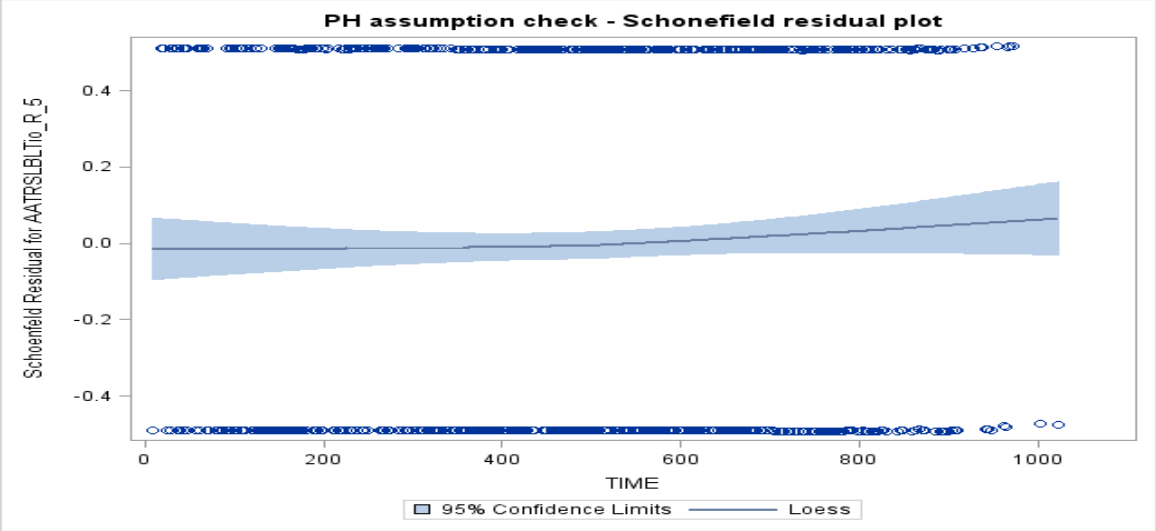
Figure 1: Assessment of Proportional Hazards Assumption: Log-Log Survival Curve



Source: Created by reviewer.

Figure 2: Assessment of Proportional Hazards Assumption: Schoenfeld Residuals Plot





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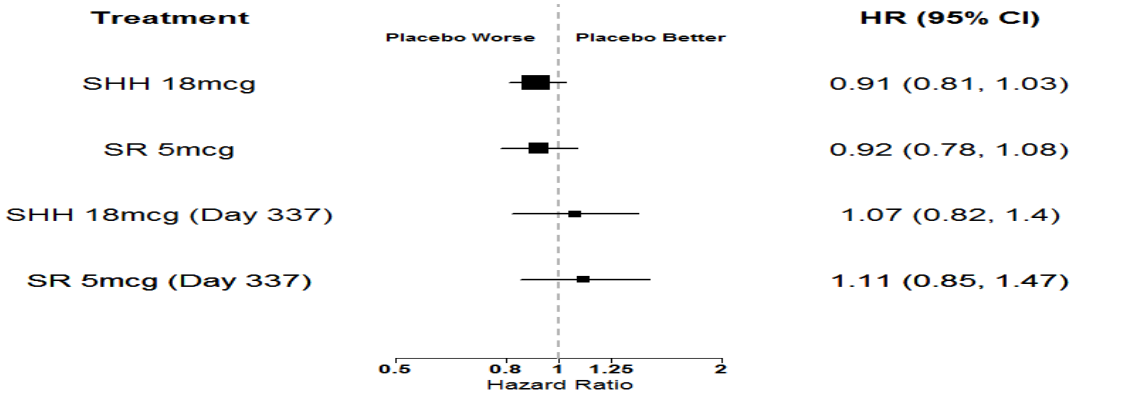
A.2 Network Meta-Analysis of Mortality

Figure 3: Forest Plot of Network Meta-analysis including UPLIFT, TIOSPIR and 4 Trials in VSD



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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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21936
Drug Name:	Spiriva Respimat
Indication(s):	Long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD)
Applicant:	Boehringer Ingelheim
Date(s):	Letter date: November 16, 2007 PDUFA date: September 16, 2008
Review Priority:	standard
Biometrics Division:	DB2
Statistical Reviewer:	Ruthanna Davi, Ph.D.
Concurring Reviewers:	Qian Li, Ph.D.
Medical Division:	Division of Pulmonary and Allergy Products
Clinical Team:	Medical Reviewer: Theresa Michele, M.D. Medical Team Leader: Sally Seymour, M.D.
Project Manager:	Miranda Raggio

Keywords:
NDA, clinical studies, mortality, safety

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

In the one-year studies, studies 254 and 255, in patients with chronic obstructive pulmonary disease (COPD), the 5 μg Spiriva Respimat and 10 μg Spiriva Respimat groups each had statistically significantly better average outcomes in terms of the four co-primary efficacy endpoints (trough FEV1 in each study, SGRQ total score in each study, TDI focal score in the prespecified pooled analysis of both studies, and number of COPD exacerbations in the prespecified pooled analysis of both studies) than the placebo group. The efficacy conclusions are robust against concerns regarding missing data as various imputation methods including the analysis with the observed data only yielded consistent conclusions.

In study 255, the risk of death was statistically significantly higher in the 10 μg Spiriva Respimat group than the placebo group. Study 254 does not confirm these findings but also may not be sufficient to refute them, as demonstrating an effect is not present is an exceedingly difficult task in a clinical study due to limited sample size and variability in observed data. Mortality for the 5 μg Spiriva Respimat group is not statistically significantly different from that of placebo in study 254. In study 255, there is no statistically significant difference in mortality in the 5 μg Spiriva Respimat group relative to placebo; however, the confidence interval for the differences between treatments is shifted towards the region favoring placebo. Thus although not statistically significantly different from placebo, these results may not be sufficient to rule out a mortality effect, given the effect seen with the higher dose.

In both of the 12-week studies, studies 251 and 252, in patients with COPD, the 5 μg Spiriva Respimat and 10 μg Spiriva Respimat groups each had statistically significantly better average trough FEV1 at 12-weeks than the placebo groups. In addition, in both of the 12-week studies, the 5 μg Spiriva Respimat and 10 μg Spiriva Respimat were each demonstrated to be noninferior to Ipratropium in terms of average trough FEV1 at 12 weeks (with a noninferiority margin of -0.05). Finally, the 10 μg Spiriva Respimat group was statistically significantly superior to Ipratropium in both of the 12-week studies while the 5 μg Spiriva Respimat group was significantly superior to Ipratropium in study 252 but not study 251. The efficacy conclusions are robust against concerns regarding missing data as analysis of the observed data only yielded supportive conclusions.

1.2 Brief Overview of Clinical Studies

The sponsor has submitted the results of two one-year (studies 254 and 255) and two 12-week (studies 251 and 252) phase III studies to support the approval of Spiriva Respimat for long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The sponsor also included two 4-week crossover studies; however, these were considered secondary to the previously mentioned pivotal studies for demonstration of efficacy and thus are not described in this document.

The one-year studies are titled, "A Randomized, Double-Blind, Placebo Controlled, Parallel Group Efficacy and Safety Comparison of One-year Treatment of Two Doses (5 μg [2 actuations of 2.5 μg] and 10 μg [2 actuations of 5 μg]) of Tiotropium Inhalation Solution Delivered by the Respimat Inhaler in Patients with Chronic Obstructive Pulmonary Disease (COPD)". The primary objective of the studies was to compare each of the two doses of Spiriva Respimat to placebo in patients with COPD, with respect to bronchodilator efficacy, effect on health status, effect on dyspnoea and effect on frequency of exacerbations. Although not the intended purpose of these studies, in this document special focus is given to the incidence of mortality in these studies as an imbalance in mortality in one of the one-year studies was observed.

The 12-week studies are titled, "A Randomized, Double-Blind, Double-Dummy, Placebo- and Active-Controlled, Parallel Group Efficacy and Safety Comparison of 12-Week Treatment of Two Doses [5 μg (2 acuations of 2.5 μg) and 10 μg (2 actuations of 5 μg)] of Tiotropium Inhalation Solution Delivered by the Respimat Inhaler, Placebo and Ipratropium Bromide Inhalation Aerosol (MDI) in Patients with Chronic Obstructive Pulmonary Disease (COPD)". The primary objective of this study was to compare the bronchodilator efficacy of each of the two doses of Spiriva Respimat once daily to placebo and to ipratropium bromide inhalation aerosol in patients with COPD.

1.3 Statistical Issues and Findings

The following statistical issues and their impact have been described in the context of the review. Please refer to the specified section for details.

1.3.1 One Year Studies (254 and 255)

- The **terminology "number of COPD exacerbations"** used to refer to one of the co-primary efficacy endpoints may be slightly misleading in that it actually refers to an incidence rate per year on a subject level. As was indicated in both the protocol and study report and just for clarity is being highlighted here, the number of COPD exacerbations for each subject is expressed per one year of exposure (assuming a constant rate of the event over the time of exposure and/or one year). That is the endpoint is calculated as the number of COPD exacerbations for a subject divided by the number of days of exposure for the same subject times 365.25 days per year. (Section 3.1.1)
- The protocol defines four co-primary efficacy endpoints. **Co-primary, in this case, is defined in the protocol to indicate that demonstrating a statistically significant difference in favor of treatment with at least one of the endpoints was to be considered adequate demonstration of efficacy.** However, for approval, Division policy would require a benefit in a pulmonary function type measurement, such as trough FEV1 (i.e., improvement in the quality of life measures alone likely would not be adequate for approval). To control the inflation of the type-I error for multiple endpoints, the hypothesis testing for these endpoints was to be conducted sequentially. To control the inflation of the type-I error for multiple doses, for each endpoint a global test of all three treatments was required to be significant before testing each of the

doses individually. **This approach is adequate to control the Type I error inflation due to multiple endpoints and multiple doses.** (Section 3.1.1)

- The "full analysis set" (FAS) was defined in the protocol and included all randomized subjects with baseline data and data following at least five days on randomized treatment for at least one primary endpoint. An **additional analysis set was defined for the primary analysis of each co-primary efficacy outcome** (except COPD exacerbations as this was not necessary due to imputation implicit in calculation of this endpoint as previously described). These were each a subset of the FAS but had the **additional requirement that subjects have data for the endpoint of interest following at least five days on randomized treatment.** The inclusion/exclusion of subjects in the SGRQ total score set and TDI focal score set are somewhat imbalanced across treatment groups. This is a potential bias in the results for these endpoints in that the unavailability of a subject's data may be related to the treatment being received; however, in this case it is likely that this bias will **favor the placebo groups** since those who are unavailable after less than five days of treatment are likely those who were dissatisfied with their assigned study treatment and if present would have provided an undesirable score on these quality of life type measures. (Sections 3.1.1 and 3.1.2.1)
- **Missing data for the trough FEV1, SGRQ total score, and TDI focal score**, three of the co-primary efficacy endpoints, resulting from a subject missing post-randomization visit(s) were, according to the protocol, to be imputed with a combination of worst-observation-carried forward and last-observation-carried forward techniques. More subjects in the placebo group relative to that in the Spiriva Respimat groups withdrew early due to worsening COPD. So that the imputation methods could result in potential bias that favors the placebo group since the unobserved data may be worse than what was imputed. However, the **efficacy comparisons appeared to be robust** as various imputations including the observed data alone yielded the same qualitative conclusions. (Sections 3.1.1 and 3.1.2.2)
- Although not explicitly described as a missing data imputation, **missing data for the number of COPD exacerbations** is handled through calculation of the endpoint by assuming that for subjects who prematurely discontinue the study, the rate of the endpoint is the same in the time period the subject was observed and the remaining portion of the study when the subject was not observed. This could bias the by-treatment group comparisons as generally, more placebo patients discontinue the study early than do active treatment group patients. However, this **bias would likely favor the placebo group** in that those who are dropping out early could be those who are more seriously impaired and/or with deteriorating conditions and thus would have higher event rates after dropping out of the study than before. (Section 3.1.1)
- The **differences between the 5 µg Spiriva Respimat group and placebo and the 10 µg Spiriva Respimat group and placebo were statistically significantly in favor of the Respimat groups for all primary efficacy comparisons** (i.e., for trough FEV1 in both studies, SGRQ total score in both studies, TDI focal score in the pooled analysis of both studies, and number of COPD exacerbations in the pooled analysis of both studies). Although not part

of the primary efficacy analysis, note that the difference in the number of COPD exacerbations was statistically significantly in favor of each of the Respimat groups over placebo in study 255 but not in study 254. (Section 3.1.2.2)

- An imbalance in mortality in one of the one-year studies was observed and the sponsor completed an extensive effort to obtain vital status for subjects who withdrew from the studies early. Vital status data is now available for approximately 98% of subjects in all treatment groups so that the possibility of a "healthy survivor effect" being displayed in the placebo group is unlikely. However, **many of the subjects who discontinued early and whose vital status was subsequently determined had been receiving COPD treatment outside of the studies that included the approved Spiriva Handihaler**. If there truly is a mortality effect associated with the use of tiotropium bromide, the mortality rates in the patients who dropped out could be elevated by the use of Spiriva Handihaler. This could **cause a bias in favor of the Spiriva Respimat treatment groups** being that more placebo subjects dropped out than active treatment group subjects. Although analyzing the mortality data without including the retrospective follow-up data might be suggested to mitigate this bias, analyzing the data observed during the course of the study alone is also biased due to the differentially higher dropout of subjects in the placebo groups possibly leading to a "healthy survivor effect". Thus both types of analyses are considered in this document. (Section 3.1.2.3)
- In study 255, the **risk of death in the 10 µg Spiriva Respimat group** was five times as likely as in the placebo group (i.e., the point estimate for the relative risk was 5.0). With 97.5% confidence, we conclude that death for those receiving 10 µg Spiriva Respimat is at least 1.1 times as likely as for those receiving placebo (i.e., the lower limit of the confidence interval for the relative risk is 1.1) and could be as much as 22.9 times as likely (i.e., the upper limit of the confidence interval for the relative risk is 22.9). Analysis of the excess incidence yields similar conclusions indicating with 97.5% confidence that at least two additional deaths and as many as 41 additional deaths should be expected in 1000 patient years of exposure to 10 µg Spiriva Respimat relative to placebo. Study 254 does not confirm these findings but also may not be sufficient to refute them, as demonstrating an effect is not present is an exceedingly difficult task in a clinical study due to limited sample size and variability in observed data. Study 254 is sufficient to demonstrate, with 97.5% confidence, that the risk of death with 10 µg Spiriva Respimat could be as much as 2.9 times as likely as with placebo and the excess number of deaths in 1000 patient years of exposure to 10 µg Spiriva Respimat relative to placebo could reach 21. (Section 3.1.2.3)
- **Mortality for the 5 µg Spiriva Respimat group** is not statistically significantly different from that of placebo in study 254. In study 255, there is no statistically significant difference in mortality in the 5 µg Spiriva Respimat group relative to placebo; however, the confidence intervals for the differences between treatments are shifted towards the region favoring placebo. Thus although not statistically significantly different from placebo, these results may not be sufficient to rule out a mortality effect, given the effect seen with the higher dose. (Section 3.1.2.3)

1.3.2 Twelve Week Studies (251 and 252)

- A **sequence of hypothesis testing** was used to first test the superiority of each Spiriva dose over placebo, then the noninferiority of each dose of Spiriva to ipratropium bromide, and finally the superiority of each dose of Spiriva to ipratropium bromide. This approach **adequately controlled the Type I error rate**. (Section 3.2.1)
- **Missing data** resulting from a subject missing post-randomization visit(s) were, according to the protocol, to be imputed with a combination of worst-observation-carried forward and last-observation-carried forward techniques. **Efficacy comparisons appeared to be robust** to these imputations as the observed data alone yielded the same qualitative conclusions as that of the data with imputation. (Section 3.2.1 and 3.2.2.2)
- Both the **5 μg Spiriva Respimat group and 10 μg Spiriva Respimat group were statistically significantly superior to placebo in terms of the primary efficacy endpoint**, trough FEV1, in both studies. Both the **5 μg Spiriva Respimat group and 10 μg Spiriva Respimat group were noninferior to Ipratropium bromide in terms of the primary efficacy endpoint**, trough FEV1, in both studies. The **10 μg Spiriva Respimat group was statistically significantly superior to Ipratropium Bromide in terms of the primary efficacy endpoint**, trough FEV1, in both studies. The **5 μg Spiriva Respimat group was statistically significantly superior to Ipratropium Bromide in terms of the primary efficacy endpoint**, trough FEV1, in study 252 but not in study 251. (Section 3.2.2.2)

2. INTRODUCTION

2.1 Overview

The sponsor has submitted the results of two one-year and two 12-week phase III studies to support the approval of Spiriva Respimat for long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

Although not available at the time of NDA submission, the Division is aware of the sponsor's recently completed four-year study (referred to as UPLIFT, Understanding the Potential for Long-Term Impact on Function with Tiotropium) comparing Spiriva Handihaler, a similar product to Spiriva Respimat, to placebo. Although not the intended purposed of this study, these results may be useful in addressing the imbalance in mortality observed in study 255. However, as these data are not included in the NDA submission, this study is not discussed in this document.

2.2 Data Sources

The sponsor has submitted the results of two one-year and two 12-week phase III studies to support the approval of Spiriva Respimat for long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including

chronic bronchitis and emphysema. The following data sets were submitted electronically and utilized in the review of these studies.

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All submitted data sets were found to be adequately documented and organized.

3. STATISTICAL EVALUATION

3.1 One-Year Studies (254 and 255)

3.1.1 Study Design (254 and 255)

Studies 254 and 255 were identically-designed, double-blind, placebo controlled, parallel group, multinational studies with a 48-week treatment period. The primary objective of the studies was to compare each of two doses (5 µg and 10 µg) of Spiriva Respimat to placebo in patients with COPD, with respect to bronchodilator efficacy, effect on health status, effect on dyspnoea and effect on frequency of exacerbations.

Following an initial screening, patients entered a two-week run-in period. Patients who successfully completed this phase were randomized into the one-year (48 week), double-blind treatment period of the study in which they received 5 µg Spiriva Respimat, 10 µg Spiriva Respimat, or placebo. For enrollment in the study, specific spirometric requirements were established to help ensure that the study population consisted of patients with relatively stable, moderate to severe COPD. In addition, all patients were to have a significant smoking history and be at least 40 years of age. For a full listing of inclusion and exclusion criteria, the reader is referred to the study protocol. Randomized treatment assignment was conducted in blocks of six with equal allocation of the three treatment groups within each block. Randomization was balanced within each center by assigning whole blocks to centers. Additional visits were to be scheduled after 2, 8, 16, 24, 32, 40, and 48 weeks of treatment.

The following are the protocol-specified four co-primary efficacy endpoints.

(1.) trough forced expiratory volume in one second (FEV1) at the end of the 48-week treatment period (Trough FEV1 was measured at the -10 minute time point at the end of the dosing interval 24 hours post drug administration)

(2.) St. Georges's Respiratory Questionnaire (SGRQ) total score at the end of the 48-week treatment period (SGRQ is a self-administered health related quality of life measure which is divided into three components: symptoms, activity, and impacts. Scores ranging from 0 to 100 are calculated for each component and

the total score. A zero score indicates no impairment of quality of life. Higher scores indicate poorer health.)

(3.) Mahler Transition Dyspnoea Index (TDI) focal score at the end of the 48-week treatment period (The Mahler TDI is a structure interview administered by trained medical personnel with three domains, functional impairment, magnitude of task, and magnitude of effort. The TDI scores for each domain range from -3 indicating major deterioration to +3 indicating major improvement. The sum of all domains yields the TDI focal score (i.e., range of -9 to +9).)

(4.) Number of COPD exacerbations in one year

- COPD exacerbations were defined (per amendment 1 to the protocol) 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 or symptoms" was further defined as a new onset or worsening of two or more of the following: shortness of breath/dyspnoea/shallow, rapid breathing, volume of sputum produced, occurrence of purulent sputum, cough, wheezing, and chest tightness. The "change in treatment" meant the use of prescribed antibiotics or corticosteroids, a significant change in prescribed respiratory medication (bronchodilators, including theophylline), or both.
- Note that the terminology "number of COPD exacerbations" may be slightly misleading in that it actually refers to an incidence rate per year on a subject level. As was indicated in both the protocol and study report and just for clarity is being highlighted here, the number of COPD exacerbations for each subject is expressed per one year of exposure (assuming a constant rate of the event over the time of exposure and/or one year). That is the endpoint is calculated as the number of COPD exacerbations for a subject divided by the number of days of exposure for the same subject times 365.25 days per year.

The protocol also specified that the first two of the endpoints (i.e., trough FEV1 and SGRQ total score) were to be analyzed separately for each study. The remaining two (i.e., Mahler TDI focal score and COPD exacerbations) were to be analyzed pooling the studies. Co-primary, in this case, is used to indicate that demonstrating a statistically significant difference in favor of treatment with at least one of the endpoints was to be considered adequate demonstration of efficacy. However, for approval, Division policy would require a benefit in a pulmonary function type measurement, such as trough FEV1 (i.e., improvement in the quality of life measures alone likely would not be adequate for approval). To control the inflation of the type-I error for multiple endpoints, the hypothesis testing for these endpoints was to be conducted sequentially in the order the endpoints are listed above. That is testing of a dose for an endpoint is only allowed when that dose has shown significant efficacy for all previous endpoints. In order to progress to testing a dose in terms of the endpoints requiring that the studies be pooled, the dose must have shown statistical significance for all previous endpoints in both studies. To control the inflation of the type-I error for multiple doses, for each endpoint a global test (i.e. F-test from ANCOVA model described below or Kruskal-Wallis test depending on the endpoint) of all three treatments was required to be significant before testing each of the doses individually.

The protocol-specified primary analysis of the trough FEV1, SGRQ total score, and Mahler TDI focal score was to be conducted using analysis of covariance (ANCOVA) with fixed effects for smoking status at trial entry (current or ex-smoker), pooled center, and treatment and baseline as a linear covariate. First, the global test was to be carried out using the F-test resulting from the ANCOVA model including all treatment groups. If significant, then the comparison of each dose of Spiriva Respimat to placebo was to be made using the pairwise comparisons resulting from the same ANCOVA model.

The protocol-specified primary analysis of the number of COPD exacerbations was to be tested as follows. First, the global test was to be carried out using the Kruskal-Wallis test. If significant, then the comparison of each dose of Spiriva Respimat to placebo was to be made using the Wilcoxon-Mann-Whitney test.

The "full analysis set" (FAS) was defined in the protocol and included all randomized subjects with baseline data and data following at least five days on randomized treatment for at least one primary endpoint. An additional analysis set was defined for the primary analysis of each co-primary efficacy outcome (except COPD exacerbations as this was not necessary due to imputation implicit in calculation of this endpoint as previously described). These were each a subset of the FAS but had the additional requirement that subjects have data for the endpoint of interest following at least five days on randomized treatment. Requiring that subjects have available data in order to be included in an analysis could bias that analysis in that the unavailability of a subject's data may be related to the treatment being received. The reader is referred to Table 2 in Section 3.2.1 for a display of the number of subjects in each protocol-specified analysis set for the primary efficacy analyses.

Missing data resulting from a subject missing post-randomization visit(s) were, according to the protocol, to be imputed as follows for each of the co-primary efficacy endpoints.

- Trough FEV1: Data missing because the patient withdrew due to worsening of COPD was to be replaced by the least favorable prior observation (i.e., the lowest trough FEV1 recorded at any time point on any previous test-day (excluding the screening visit). Missing data for subjects who did not withdrawal due to worsening of COPD was to be replaced by the data from the corresponding time point at the most recent non-missing visit (i.e., last-observation carried-forward (LOCF)).
- SGRQ total score: Missing SGRQ data will be imputed by the LOCF rule which is consistent with the methods used in the validation of the questionnaire.
- TDI focal score: If missing because the patient withdrew due to worsening of COPD, the worst (i.e., the lowest score in the scale of possible responses) was to be imputed. Otherwise LOCF rule was to be applied.
- COPD exacerbations: Imputation is achieved through calculation of the endpoint by assuming that for subjects who prematurely discontinue the study, the rate of the endpoint is the same in the time period the subject was observed and the remaining portion of the study when the subject was not observed. The number of COPD exacerbations for each subject is to be expressed per one year of exposure. That is the endpoint is calculated as the number of COPD exacerbations for a subject divided by the number of days of exposure for the same subject (whether the entire length of the study or something less than that) times 365.25 days per year.

3.1.2 Results (254 and 255)

3.1.2.1 Discontinuations, Analysis Sets, and Baseline Characteristics (254 and 255)

Studies 254 and 255 randomized 983 and 1007 subjects, respectively. In study 254, 319 were assigned placebo, 332 were assigned 5 µg Spiriva Respimat, and 332 were assigned to 10 µg Spiriva Respimat. In study 255, 334 were assigned placebo, 338 were assigned 5 µg Spiriva Respimat, and 335 were assigned to 10 µg Spiriva Respimat.

Summary of the subject disposition is given in Table 1. The proportion of subjects prematurely discontinuing study medication was higher in the placebo group than the treatment groups in both studies (29% versus 17% and 17% in study 254 and 34% versus 18% and 24% in study 255). The most common reason in all treatment groups and both studies for premature discontinuation of study medication was COPD worsening.

Table 1: Subject Discontinuations

	Study 254			Study 255		
	Placebo N=319	**5µg Spiriva N=332**	**10µg Spiriva N=332**	**Placebo N=334**	**5µg Spiriva N=338**	**10µg Spiriva N=335**
Total Completed	**228 (71%)**	**277 (83%)**	**277 (83%)**	**220 (66%)**	**278 (82%)**	**254 (76%)**
Total Prematurely Disc. Study Med.	**91 (29%)**	**55 (17%)**	**55 (17%)**	**114 (34%)**	**60 (18%)**	**81 (24%)**
COPD worsening	33 (10%)	13 (4%)	12 (4%)	59 (18%)	18 (5%)	22 (7%)
Worsening of other pre-existing disease	3 (1%)	2 (1%)	2 (1%)	3 (1%)	1 (<1%)	2 (1%)
Other AE	12 (4%)	16 (5%)	18 (5%)	12 (4%)	17 (5%)	23 (7%)
Protocol Noncomp.	4 (1%)	2 (1%)	2 (1%)	11 (3%)	6 (2%)	11 (3%)
Lost to follow-up	11 (3%)	4 (1%)	5 (2%)	4 (1%)	5 (1%)	6 (2%)
Consent withdrawn	19 (6%)	12 (4%)	9 (3%)	19 (6%)	7 (2%)	14 (4%)
Other	9 (3%)	6 (2%)	7 (2%)	6 (2%)	6 (2%)	3 (1%)

Source: Clinical Study Report, Studies 254 and 255, Table 10.1:1 (with modifications in format)

Table 2 displays the analysis sets for the co-primary efficacy outcomes (except COPD exacerbations as this was not necessary due to imputation implicit in calculation of this endpoint – see Section 3.1.1 for further comment). The FAS was defined in the protocol and includes all randomized subjects with baseline data and data following at least five days on randomized treatment for at least one primary endpoint. The remaining analysis sets were also defined in the protocol and are each subsets of the FAS but require that subjects have data for the endpoint of interest following at least five days on randomized treatment.

Table 2: Analysis Sets						
	Study 254			Study 255		
	Placebo N=319	5µg Spiriva N=332	10µg Spiriva N=332	Placebo N=334	5µg Spiriva N=338	10µg Spiriva N=335
Full Analysis Set (FAS)	**297 (93%)**	**327 (98%)**	**323 (97%)**	**311 (93%)**	**327 (97%)**	**326 (97%)**
Trough FEV1 set	296 (93%)	326 (98%)	320 (96%)	307 (92%)	324 (96%)	324 (97%)
SGRQ total score set	275 (86%)	318 (96%)	315 (95%)	276 (83%)	310 (92%)	304 (91%)
TDI focal score set	273 (86%)	318 (96%)	313 (94%)	279 (84%)	310 (92%)	305 (91%)

Source: Clinical Study Report Appendix, Studies 254 and 255, Table 15.1.3:1 (with modifications in format)

The inclusion/exclusion of subjects in the FAS and trough FEV1 set are fairly balanced across treatment groups, with only slightly fewer (proportionally) placebo subjects included than treatment group subjects. The SGRQ total score set and TDI focal score set are more imbalanced across treatment groups with approximately 85% of placebo subjects included compared to approximately 92% of those in the Spiriva groups. This is a potential bias in the results for these endpoints in that the unavailability of a subject's data may be related to the treatment being received; however, in this case it is likely that this bias will favor the placebo groups since those who are unavailable after less than five days of treatment are likely those who were dissatisfied with their assigned study treatment and if present would have provided an undesirable score on these quality of life type measures.

Demographic and other baseline characteristics for all randomized subjects are given in Table 3. As would be expected due to the virtues of random treatment assignment, the overall demographic and baseline characteristics profile was balanced across the treatment groups.

Table 3: Demographic and Other Baseline Characteristics (All Randomized)						
	Study 254			Study 255		
	Placebo N=319	5µg Spiriva N=332	10µg Spiriva N=332	Placebo N=334	5µg Spiriva N=338	10µg Spiriva N=335
Gender – n(%)						
Male	252 (79%)	243 (73%)	252 (76%)	235 (70%)	248 (73%)	246 (73%)
Female	67 (21%)	89 (27%)	80 (24%)	99 (30%)	90 (27%)	89 (27%)
Race – n(%)						
Missing	19 (6%)	22 (7%)	19 (6%)	26 (8%)	24 (7%)	25 (8%)
White	292 (92%)	304 (92%)	311 (94%)	302 (90%)	307 (91%)	302 (90%)
Black	8 (3%)	5 (2%)	1 (<1%)	6 (2%)	2 (1%)	7 (2%)
Asian	0 (0%)	1 (<1%)	1 (<1%)	0 (0%)	5 (2%)	1 (<1%)
Age (yrs) – mean±stdev	65±9	65±8	65±8	66±8	64±9	66±9
Smoking history – n (%)						
Ex-smoker	217 (68%)	208 (63%)	209 (63%)	200 (60%)	208 (62%)	226 (68%)
Smoker	102 (32%)	124 (37%)	123 (37%)	134 (40%)	130 (39%)	109 (33%)
Smoking (pk. yrs) – mean±stdev	46±25	47±29	50±28	49±27	47±25	48±26
Duration of COPD (yrs) -- mean±stdev	10±8	9±7	9±8	9±7	8±6	9±7

Source: Clinical Study Report, Studies 254 and 255, Table 11.2:1 (with modifications in format)

3.1.2.2 Efficacy Analyses (254 and 255)

Trough FEV1

The first co-primary efficacy endpoint for these studies was trough FEV1 at the end of 48 weeks of treatment.

The global hypothesis test for any difference among all three treatment groups in this endpoint was statistically significant ($p<0.0001$) thus allowing the comparisons of each dose with placebo for trough FEV1 in accordance with the protocol-specified multiplicity plan.

Comparisons of each dose of Spiriva Respimat to placebo for trough FEV1 using the protocol-specified ANCOVA model are given in Table 4. The differences between the 5 µg Spiriva Respimat group and placebo and the 10 µg Spiriva Respimat group and placebo were both statistically significant ($p<0.0001$ in all cases).

The results for trough FEV1 using the observed data only (without imputation of the missing data) are consistent with these conclusions indicating that the results of the primary efficacy analysis for this endpoint likely are not an artifact of missing data.

Table 4: Trough FEV1 (L) at 48 weeks – First Co-Primary Efficacy Endpoint [1,2]

	Study 254			Study 255		
	Placebo N=296	5µg Spiriva N=326	10µg Spiriva N=320	Placebo N=307	5µg Spiriva N=324	10µg Spiriva N=324
Least Squares Means	1.03	1.17	1.19	1.02	1.14	1.16
Difference from Placebo		0.14	0.16		0.11	0.14
95% CI for difference		(0.10, 0.18)	(0.12, 0.20)		(0.08, 0.15)	(0.11, 0.18)
p-value for comparison to placebo		<0.0001	<0.0001		<0.0001	<0.0001

1. Analyses based on protocol-specified ANCOVA model with terms for treatment, smoking status at entry, center, and baseline.
2. As per-protocol, data after rescue use or missing due to worsening of COPD are imputed using the worst observation carried forward, otherwise missing data are imputed using LOCF.

Source: Clinical Study Report Appendix, Studies 254 and 255, Tables 15.2.1:2 and 15.2.1:6 (with modifications in format)

SGRQ total score

The second co-primary efficacy endpoint for these studies was the SGRQ total score at the end of 48 weeks of treatment.

The global hypothesis test for any difference among all three treatment groups in this endpoint was statistically significant ($p<0.0001$) and the comparisons of each dose of Spiriva Respimat to placebo for trough FEV1 were both statistically significant thus allowing the comparisons of each dose with placebo for SGRQ total score in accordance with the protocol-specified multiplicity plan.

Comparisons of each dose of Spiriva Respimat to placebo for the SGRQ total score using the protocol-specified ANCOVA model are given in Table 5. The differences between the 5 µg Spiriva Respimat group and placebo and the 10 µg Spiriva Respimat group and placebo were both statistically significant (p=0.001 and p<0.0001, respectively in study 254 and p=0.0004 and p=0.001, respectively in study 255).

The results for the SGRQ total score using the observed data only (without imputation of the missing data) are consistent with these conclusions indicating that the results of the primary efficacy analysis for this endpoint likely are not an artifact of missing data.

Table 5: SGRQ Total Score – Second Co-Primary Efficacy Endpoint [1,2]

	Study 254			Study 255		
	Placebo N=275	5µg Spiriva N=318	10µg Spiriva N=315	Placebo N=276	5µg Spiriva N=310	10µg Spiriva N=304
Least Squares Means	42.9	39.6	38.7	43.5	39.8	40.0
Difference from Placebo		-3.3	-4.2		-3.7	-3.4
95% CI for difference		(-5.2, -1.3)	(-6.2, -2.3)		(-5.8, -1.6)	(-5.5, -1.4)
p-value for comparison to placebo		0.001	<0.0001		0.0004	0.001

1. Analyses based on protocol-specified ANCOVA model with terms for treatment, smoking status at entry, center, and baseline.
2. As per-protocol, missing data are imputed using LOCF.

Source: Clinical Study Report Appendix, Studies 254 and 255, Tables 15.2.2:1 and 15.2.2:2 (with modifications in format)

TDI focal score

The third co-primary efficacy endpoint for these studies was the TDI focal score at the end of 48 weeks of treatment. The protocol specified that the primary analysis of this endpoint should be conducted using the data from studies 254 and 255 pooled.

The global hypothesis test for any difference among all three treatment groups in this endpoint in the pooled studies was statistically significant (p<0.0001) and the comparisons of each dose of Spiriva Respimat to placebo for trough FEV1 and SGRQ total score were all statistically significant thus allowing the comparisons of each dose with placebo for TDI focal score in accordance with the protocol-specified multiplicity plan.

Comparisons of each dose of Spiriva Respimat to placebo for TDI focal score using the protocol-specified ANCOVA model are given in Table 6. The differences between the 5 µg Spiriva Respimat group and placebo and the 10 µg Spiriva Respimat group and placebo were both statistically significant (p<0.0001 in both cases). The results for the TDI focal score using the observed data only (without imputation of the missing data) are consistent with these conclusions indicating that the results of the primary efficacy analysis for this endpoint likely are not an artifact of missing data.

Table 6: TDI Focal Score – Third Co-Primary Efficacy Endpoint [1,2]			
	Study 254 and 255 Pooled		
	Placebo N=552	5µg Spiriva N=628	10µg Spiriva N=618
Least Squares Means	0.8	1.9	1.9
Difference from Placebo		1.1	1.1
95% CI for difference		(0.7, 1.4)	(0.8, 1.4)
p-value for comparison to placebo		<0.0001	<0.0001

1. Analyses based on protocol-specified ANCOVA model with terms for treatment, smoking status at entry, center, and baseline.
2. As per-protocol, data missing due to worsening of COPD are imputed using the worst observation carried forward, otherwise missing data are imputed using LOCF.
Source: Clinical Study Report Appendix, Study 9992, Tables 15.2.11:2 and 15.2.11:3 (with modifications in format)

Although not part of the primary efficacy analysis, for completeness, the results for the TDI focal score endpoint for each study is presented in Table 7. These results are consistent with that of the pooled studies.

Table 7: TDI Focal Score – Third Co-Primary Efficacy Endpoint – By Study [1,2]						
	Study 254			Study 255		
	Placebo N=273	5µg Spiriva N=318	10µg Spiriva N=313	Placebo N=279	5µg Spiriva N=310	10µg Spiriva N=305
Least Squares Means	0.8	1.9	2.0	0.9	1.9	1.8
Difference from Placebo		1.1	1.3		1.0	0.9
95% CI for difference		(0.7, 1.5)	(0.8, 1.7)		(0.5, 1.5)	(0.4, 1.4)
p-value for comparison to placebo		<0.0001	<0.0001		<0.0001	0.0002

1. Analyses based on protocol-specified ANCOVA model with terms for treatment, smoking status at entry, center, and baseline.
2. As per-protocol, data missing due to worsening of COPD are imputed using the worst observation carried forward, otherwise missing data are imputed using LOCF.
Source: Clinical Study Report Appendix, Studies 254 and 255, Tables 15.2.11:2 and 15.2.11:3 (with modifications in format)

Number of COPD exacerbations

The fourth co-primary efficacy endpoint for these studies was the number of COPD exacerbation in one year. Note that the terminology "number of COPD exacerbations" may be slightly misleading in that it actually refers to an incidence rate per year on a subject level. As was indicated in both the protocol and study report and just for clarity is being highlighted here, the number of COPD exacerbations for each subject is expressed per one year of exposure (assuming a constant rate of the event over the time of exposure and/or one year). That is the endpoint is calculated as the number of COPD exacerbations for a subject divided by the number of days of exposure for the same subject times 365.25 days per year. The protocol specified that the primary analysis of this endpoint should be conducted using the data from studies 254 and 255 pooled.

The global hypothesis test for any difference among all three treatment groups in this endpoint in the pooled studies was statistically significant ($p<0.0001$) and the comparisons of each dose of Spiriva Respimat to placebo for trough FEV1, SGRQ total score, and TDI focal score (pooled studies) were all statistically significant thus allowing the comparisons of each dose with placebo for number of COPD exacerbations in accordance with the protocol-specified multiplicity plan.

Comparisons of each dose of Spiriva Respimat to placebo for the number of COPD exacerbations using the protocol-specified Wilcoxon-Mann-Whitney test are given in Table 8. The differences between the 5 µg Spiriva Respimat group and placebo and the 10 µg Spiriva Respimat group and placebo were both statistically significant ($p=0.002$ and $p=0.0008$, respectively).

Table 8: Number of COPD Exacerbations – Fourth Co-Primary Efficacy Endpoint

	Study 254 and 255 Pooled		
	Placebo N=653	5µg Spiriva N=670	10µg Spiriva N=667
Mean Exacerbation Rate [1]	1.91	0.93	1.02
p-value for comparison to placebo [2]		0.002	0.0008

1. Exacerbation rate = number of exacerbations in subject X divided by number of days of treatment received by subject X times 365.25 days per year. i.e., yielding exacerbation rate per year of treatment
2. Analyses based on protocol-specified Wilcoxon-Mann Whitney test.

Source: Clinical Study Report Appendix, Study 9992, Tables 15.2.12:1 (with modifications in format)

Although not part of the primary efficacy analysis, for completeness, the results for the number of COPD exacerbations for each study are presented in Table 9. These results are at least numerically consistent with that of the pooled studies.

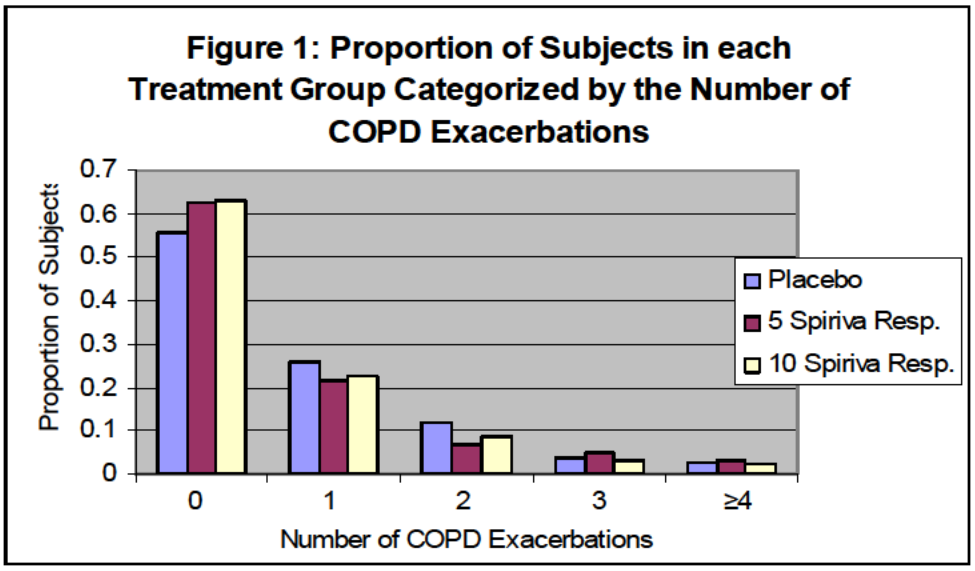
Table 9: Number of COPD Exacerbations – Fourth Co-Primary Efficacy Endpoint – By Study

	Study 254			Study 255		
	Placebo N=319	5µg Spiriva N=332	10µg Spiriva N=332	Placebo N=334	5µg Spiriva N=338	10µg Spiriva N=335
Mean Exacerbation Rate [1]	1.9	0.7	0.8	2.0	1.1	1.2
p-value for comparison to placebo [2]		0.2	0.07		0.003	0.004

1. Exacerbation rate = number of exacerbations in subject X divided by number of days of treatment received by subject X times 365.25 days per year. i.e., yielding exacerbation rate per year of treatment
2. Analyses based on protocol-specified Wilcoxon-Mann Whitney test.

Source: Documentation of Statistical Methods Appendix, Studies 254 and 255, Table 6.8.1 (with modifications in format)

The proportion of subjects in each treatment group categorized by the number of COPD exacerbations is displayed in Figure 1. This is a graphical illustration of the primary efficacy comparison made in Table 8 and points to the impact of treatment in that the proportion of subjects with no exacerbations is lowest in the placebo group while the proportions of subjects with one or two exacerbations is highest in the placebo group (and fairly balanced across treatment groups for three and four or more exacerbations).



Rescue Medication

The mean number of occasions of rescue salbutamol use was lower for both Spiriva Respimat groups compared to the placebo group throughout the trial. The differences between the 5 µg and 10 µg Spiriva Respimat groups and placebo ranged from -0.7 to -1.0 and -0.6 and -0.9, respectively for study 254 and from -0.3 to -0.9 and -0.6 to -1.0, respectively for study 255. These differences were statistically significant for all weeks except for the 5 µg Spiriva Respimat versus placebo comparison at weeks 28 and 37 in study 255.

3.1.2.3 Safety Analyses (254 and 255)

Although not the intended purpose of studies 254 and 255, special focus is given to the incidence of mortality in these studies as an imbalance in mortality in one of the one-year studies was observed.

In the last quarter of 2005, at the time of completion of studies 254 and 255, the sponsor reported to the Division that an unexpected but statistically significant imbalance in mortality favoring the placebo group over the Spiriva Respimat groups had been observed in study 255 (but not study 254). It was conjectured that the imbalance in mortality might be due to the differential dropout rates observed in these studies. That is subjects who discontinue the study early are generally more impaired as determined by their baseline FEV1 than those who continue and since the dropout rates were higher in the placebo group than the Spiriva Respimat groups, these results could be an illustration of a "healthy survivor effect" in the placebo group. For this reason, the Divison urged the sponsor to retrospectively collect the vital status for all subjects in studies 254 and 255 for whom it was unknown whether the patient was alive or dead due to his or her early study discontinuation.

With the 4-month safety update for this NDA, the sponsor has completed an extensive effort to obtain vital status information for these subjects and has provided updated analyses of the mortality data.

Table 10 describes the proportions of subjects who completed the studies (and thus vital status was known) and the proportions of subjects whose vital status information is now available (whether through the original studies or the retrospectively follow-up). Vital status data is now available for approximately 98% of subjects in all treatment groups so that the possibility of a "healthy survivor effect" being displayed in the placebo group is unlikely. However, it should be noted that many of the subjects who discontinued early and whose vital status was subsequently determined had been receiving COPD treatment outside of the studies that included the approved Spiriva Handihaler. If there truly is a mortality effect associated with the use of tiotropium bromide, the mortality rates in the patients who dropped out could be elevated by the use of Spiriva Handihaler. This could cause a bias in the current analysis being that more placebo subjects dropped out than active treatment group subjects.

Table 10: Subjects with Known Vital Status

	Study 254			Study 255		
	Placebo N=319	5µg Spiriva N=332	10µg Spiriva N=332	Placebo N=334	5µg Spiriva N=338	10µg Spiriva N=335
Study Completed	228 (72%)	277 (83%)	277 (83%)	220 (66%)	278 (82%)	254 (76%)
Vital Status Available	312 (98%)	328 (99%)	328 (99%)	323 (97%)	328 (97%)	326 (97%)

Table 11 provides analysis of the mortality data both including only the deaths collected as part of the original studies as well as including all deaths whether collected as part of the original studies or with the retrospective follow-up. These results indicate that even with the retrospective follow-up data there is a statistically significant increase in mortality in the 10 µg Spiriva Respimat group relative to placebo in study 255 while study 254 is neutral.

In study 255, the risk of death in the 10 µg Spiriva Respimat group was five times as likely as in the placebo group (i.e., the point estimate for the relative risk was 5.0). With 97.5% confidence, we conclude that death for those receiving 10 µg Spiriva Respimat is at least 1.1 times as likely as for those receiving placebo (i.e., the lower limit of the confidence interval for the relative risk is 1.1) and could be as much as 22.9 times as likely (i.e., the upper limit of the confidence interval for the relative risk is 22.9). Analysis of the excess incidence yields similar conclusions indicating with 97.5% confidence that at least two additional deaths and as many as 41 additional deaths should be expected in 1000 patient years of exposure to 10 µg Spiriva Respimat relative to placebo. Study 254 does not confirm these findings but also may not be sufficient to refute them, as demonstrating an effect is not present is an exceedingly difficult task in a clinical study due to limited sample size and variability in observed data. Study 254 is sufficient to demonstrate, with 97.5% confidence, that the risk of death with 10 µg Spiriva Respimat could be as much as 2.9 times as likely as with placebo and the excess number of deaths in 1000 patient years of exposure to 10 µg Spiriva Respimat relative to placebo could reach 21.

Mortality for the 5 µg Spiriva Respimat group is not statistically significantly different from that of placebo in study 254. In study 255, there is no statistically significant difference in mortality in the 5 µg Spiriva Respimat group relative to placebo; however, the confidence intervals for the differences between treatments are shifted towards the region favoring placebo. Thus although not statistically significantly different from placebo, these results also may not be sufficient to rule out a mortality effect, given the effect seen with the higher dose.

Table 11: Mortality by Treatment Group							
Any Fatal Adverse Event	**Placebo N=319**	**5 mcg Spiriva N=332**	**10 mcg Spiriva N=332**	**5 mcg Spiriva vs. Placebo**		**10 mcg Spiriva vs. Placebo**	
	# events (%[1])	**# events (%[1])**	**# events (%[1])**	**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.)[2]**
Study 254							
Sample Size (baseline)	319	332	332				
Within Study	5 (1.9%)	7 (2.2%)	8 (2.4%)	1.2 (0.4, 3.8)	3 (-20, 27)	1.4 (0.4, 4.2)	5 (-19, 28)
With Retro Follow-up	7 (2.3%)	8 (2.5%)	8 (2.1%)	1.1 (0.4, 3.0)	2 (-22, 26)	1.1 (0.4, 2.9)	-1 (-24, 21)
Study 255							
Sample Size (baseline)	334	338	335				
Within Study	0 (0.0%)	5 (1.6%)	8 (2.7%)	undefined	16 (2, 30)*	undefined	27 (9, 46)*
With Retro Follow-up	2 (0.6%)	7 (1.8%)	10 (2.8%)	3.4 (0.7, 16.5)	12 (-5, 28)	5.0 (1.1, 22.9)*	21 (2, 41)*
Studies 254 & 255							
Sample Size (baseline)	653	670	667				
Within Study	5 (0.9%)	12 (1.9%)	16 (2.5%)	2.1 (0.7, 5.9)	10 (-4, 23)	2.9 (1.1, 8.0)*	16 (1, 31)*
Retro Follow-up	9 (1.4%)	15 (2.1%)	18 (2.5%)	1.6 (0.7, 3.6)	7 (-7, 21)	1.9 (0.9, 4.3)	10 (-5, 25)

3.2 Twelve-Week Studies (251 and 252)

3.2.1 Study Design (251 and 252)

Studies 251 and 252 were identically-designed, double-blind, double-dummy, parallel group, multinational studies with a 12-week treatment period. The primary objective of the studies was to compare the bronchodilator efficacy of each of two doses (5 μg and 10 μg) of Spiriva Respimat to placebo and ipratropium bromide inhalation aerosol (MDI) in patients with COPD.

Following an initial screening, patients entered a two-week run-in period. Patients who successfully completed this phase were randomized into the 12-week, double-blind treatment period of the study in which they received 5 μg Spiriva Respimat, 10 μg Spiriva Respimat, placebo, or ipratropium bromide inhalation aerosol. For enrollment in the study, specific spirometric requirements were established to help ensure that the study population consisted of patients with relatively stable, moderate to severe COPD. In addition, all patients were to have a significant smoking history and be at least 40 years of age. For a full listing of inclusion and exclusion criteria, the reader is referred to the study protocol. Randomized treatment assignment was conducted in blocks of four with equal allocation of the four treatment groups within each block. Randomization was balanced within each center by assigning whole blocks to centers. Additional visits were to be scheduled after 1, 4, 8, and 12 weeks of treatment.

The protocol-specified primary efficacy endpoint was trough forced expiratory volume in one second (FEV1) at the end of the 12-week treatment period. Trough FEV1 was measured at the -10 minute time point at the end of the dosing interval 24 hours post drug administration. Analysis of covariance (ANCOVA) with terms for smoking status (current or ex-smoker at study entry), center, and treatment with baseline as a continuous covariate was the protocol-specified primary analysis method. The following sequence of hypothesis testing was used to first establish the superiority of each Spiriva dose over placebo, then the noninferiority of each dose of Spiriva to ipratropium bromide, and finally the superiority of each dose of Spiriva to ipratropium bromide.

Step 1: 10 μg Spiriva Respimat versus placebo (superiority)
Step 2: 5 μg Spiriva Respimat versus placebo (superiority)
Step 3: 10 μg Spiriva Respimat versus ipratropium bromide (noninferiority with pre-specified noninferiority margin of 0.05L)
Step 4: 5 μg Spiriva Respimat versus ipratropium bromide (noninferiority with pre-specified noninferiority margin of 0.05L)
Step 5: 10 μg Spiriva Respimat versus ipratropium bromide (superiority)
Step 6: 5 μg Spiriva Respimat versus ipratropium bromide (superiority)

By requiring that all previous steps be statistically significant to consider the next step confirmatory, the type I error was controlled.

The "full analysis set" (FAS) was defined in the protocol and included all randomized subjects with baseline data and data following at least five days on randomized treatment for the primary endpoint, trough FEV1.

Missing data resulting from a subject missing post-randomization visit(s) were, according to the protocol, to be imputed as follows. Data missing because the patient withdrew due to worsening of COPD was to be replaced by the least favorable prior observation (i.e., the lowest trough FEV1 recorded at any time point on any previous test-day (excluding the screening visit). Missing data for subjects who did not withdrawal due to worsening of COPD was to be replaced by the data from the corresponding time point at the most recent non-missing visit (i.e., last-observation carried-forward (LOCF)).

3.2.2 Results (251 and 252)

3.2.2.1 Discontinuations, Analysis Sets, and Baseline Characteristics (251 and 252)

Studies 251 and 252 randomized 361 and 358 subjects, respectively. In study 251, 91 were assigned placebo, 88 were assigned 5 µg Spiriva Respimat, 93 were assigned to 10 µg Spiriva Respimat, and 89 were assigned ipratropium. In study 252, 90 were assigned placebo, 92 were assigned 5 µg Spiriva Respimat, 87 were assigned to 10 µg Spiriva Respimat, and 89 were assigned ipratropium.

Summary of the subject disposition is given in Table 12. The proportion of subjects prematurely discontinuing study medication was higher in the ipratropium group than the treatment groups in both studies (19% versus 9% and 10% in study 251 and 16% versus 9% and 10% in study 252). In study 252, the study medication discontinuation rate was also higher in the placebo group than the treatment groups (17% versus 9% and 10%).

Table 12: Subject Discontinuations

	Study 251				Study 252			
	Placebo N=91	5µg Spiriva N=88	10µg Spiriva N=93	Ipratro. N=89	Placebo N=90	5µg Spiriva N=92	10µg Spiriva N=87	Ipratro. N=89
Total Completed	**84 (92%)**	**80 (91%)**	**84 (90%)**	**72 (81%)**	**75 (83%)**	**84 (91%)**	**78 (90%)**	**75 (84%)**
Total Prematurely Disc. Study Med.	**7 (8%)**	**8 (9%)**	**9 (10%)**	**17 (19%)**	**15 (17%)**	**8 (9%)**	**9 (10%)**	**14 (16%)**
COPD worsening	4 (4%)	3 (3%)	1 (1%)	9 (10%)	7 (8%)	3 (3%)	2 (2%)	2 (2%)
Worsening of other pre-existing disease	0 (0%)	1 (1%)	1 (1%)	0 (0%)	0 (0%)	1 (1%)	2 (2%)	1 (1%)
Other AE	1 (1%)	2 (2%)	3 (3%)	2 (2%)	4 (4%)	3 (3%)	3 (3%)	7 (8%)
Protocol Noncomp.	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lost to follow-up	1 (1%)	2 (2%)	3 (3%)	2 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Consent withdrawn	1 (1%)	0 (0%)	1 (1%)	3 (3%)	2 (2%)	0 (0%)	2 (2%)	3 (3%)
Other	0 (0%)	0 (0%)	0 (0%)	1 (1%)	2 (2%)	1 (1%)	0 (0%)	1 (1%)

Source: Clinical Study Report, Studies 251 and 252, Table 10.1:1 (with modifications in format)

Table 13 displays the FAS used in the primary efficacy analysis. The FAS was defined in the protocol and includes all randomized subjects with baseline data and data following at least five days on randomized treatment for the primary endpoint, trough FEV1.

Table 13: Full Analysis Set								
	Study 251				Study 252			
	Placebo N=91	5µg Spiriva N=88	10µg Spiriva N=93	Ipratro. N=89	Placebo N=90	5µg Spiriva N=92	10µg Spiriva N=87	Ipratro. N=89
Full Analysis Set	**87 (96%)**	**85 (97%)**	**89 (96%)**	**84 (94%)**	**84 (93%)**	**90 (98%)**	**84 (97%)**	**86 (97%)**

Source: Clinical Study Report Appendix, Studies 254 and 255, Table 15.1.3:1 (with modifications in format)

The inclusion/exclusion of subjects in the FAS are fairly balanced across treatment groups, with only slightly fewer (proportionally) placebo subjects included than treatment group subjects in study 252.

Demographic and other baseline characteristics for all randomized subjects are given in Table 14. As would be expected due to the virtues of random treatment assignment, the overall demographic and baseline characteristics profile was balanced across the treatment groups.

Table 14: Demographic and Other Baseline Characteristics (All Randomized)								
	Study 251				Study 252			
	Placebo N=91	5µg Spiriva N=88	10µg Spiriva N=93	Ipratro. N=89	Placebo N=90	5µg Spiriva N=92	10µg Spiriva N=87	Ipratro. N=89
Gender – n(%)								
Male	70 (77%)	61 (69%)	69 (74%)	69 (78%)	55 (61%)	64 (70%)	60 (69%)	51 (57%)
Female	21 (23%)	27 (31%)	24 (26%)	20 (23%)	35 (39%)	28 (30%)	27 (31%)	38 (43%)
Race – n(%)								
White	91 (100%)	87 (99%)	91 (98%)	89 (100%)	85 (94%)	89 (97%)	80 (92%)	88 (99%)
Black	0 (0%)	1 (1%)	1 (1%)	0 (0%)	5 (5.6%)	2 (2%)	7 (8%)	0 (0%)
Asian	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Age (yrs) – mean±stdev	62±9	63±8	61±9	62±8	65±8	66±10	66±9	68±7
Smoking history – n (%)								
Ex-smoker	48 (53%)	50 (57%)	58 (62%)	51 (57%)	56 (62%)	64 (70%)	55 (63%)	56 (63%)
Smoker	43 (47%)	38 (43%)	35 (38%)	38 (43%)	34 (38%)	28 (30%)	32 (37%)	33 (37%)
Smoking (pk. yrs) – mean±stdev	42±24	43±26	42±22	43±26	60±33	60±32	65±35	54±22
Duration of COPD (yrs) -- mean±stdev	10±8	10±8	9±7	10±7	8.6±7	10±7	10±10	10±6

Source: Clinical Study Report, Studies 251 and 252, Table 11.2:1 (with modifications in format)

3.2.2.2 Efficacy Analyses (251 and 252)

The primary efficacy endpoint for these studies was trough FEV1 response at the end of 12 weeks of treatment.

Comparisons of each dose of Spiriva Respimat to placebo and Ipratropium for trough FEV1 using the protocol-specified ANCOVA model are given in Table 15. Comparisons that are

considered statistically significant, in accordance with the protocol-specified hypothesis testing sequence to control type I error, are shaded.

> Step 1: The 10 µg Spiriva Respimat group is statistically significantly superior to placebo in both studies ($p<0.0001$ and $p=0.0001$ in studies 251 and 252, respectively). The statistical significance in this step (in each study) allows testing of step 2 to be considered confirmatory (for each study).
> Step 2: The 5 µg Spiriva Respimat group is statistically significantly superior to placebo in both studies ($p=0.003$ and $p<0.0001$ in studies 251 and 252, respectively). The statistical significance of this step and the previous step (in each study) allows testing of step 3 to be considered confirmatory (for each study).
> Step 3: The 10 µg Spiriva Respimat group is noninferior to Ipratropium in both studies ($p<0.0001$ in both studies) indicating that the 10 µg Spiriva Respimat trough FEV1 is at most 0.05L (i.e., the pre-specified noninferiority margin) smaller than that of Ipratropium. The statistical significance in this step and the previous steps (in each study) allows testing of step 4 to be considered confirmatory (for each study).
> Step 4: The 5 µg Spiriva Respimat group is noninferior to Ipratropium in both studies ($p=0.004$ and $p<0.0001$ in studies 251 and 252, respectively) indicating that the 5 µg Spiriva Respimat trough FEV1 is at most 0.05L (i.e., the pre-specified noninferiority margin) smaller than that of Ipratropium.. The statistical significance of this step and the previous steps (in each study) allows testing of step 5 to be considered confirmatory (for each study).
> Step 5: The 10 µg Spiriva Respimat group is statistically significantly superior to Ipratropium in both studies ($p=0.002$ and $p=0.01$ in studies 251 and 252). The statistical significance in this step and the previous steps (in each study) allows testing of step 4 to be considered confirmatory (for each study).
> Step 6: In study 251, the 5 µg Spiriva Respimat group is not statistically significantly superior to Ipratropium ($p=0.2$). In study 252, however, the 5 µg Spiriva Respimat group is statistically significantly superior to Ipratropium ($p=0.006$).

The results for trough FEV1 using the observed data only (without imputation of the missing data) are consistent with these conclusions indicating that the results of the primary efficacy analysis for this endpoint likely are not an artifact of missing data.

Table 15: Trough FEV1 Response at 12 weeks –Primary Efficacy Endpoint [1,2]								
	Study 251				Study 252			
	Placebo N=87	5µg Spiriva N=85	10µg Spiriva N=89	Ipratro. N=94	Placebo N=93	5µg Spiriva N=90	10µg Spiriva N=84	Ipratro. N=86
Least Squares Means	1.23	1.34	1.41	1.29	0.99	1.11	1.10	1.03
Diff from Placebo		0.11	0.18			0.12	0.12	
95% CI for diff. from placebo		(0.04, 0.18)	(0.11, 0.25)			(0.07, 0.18)	(0.06, 0.17)	
p-value for comparison to placebo (superiority)		0.003	<0.0001			<0.0001	0.0001	
Diff from Ipratropium		0.05	0.12			0.08	0.07	
95% CI for diff. from Ipratropium		(-0.02, 0.12)	(0.05, 0.19)			(0.02, 0.14)	(0.01, 0.13)	
p-value for comparison to Ipratropium (noninferiority)		0.004	<0.0001			<0.0001	<0.0001	
p-value for comparison to Ipratropium (superiority)		0.2	0.002			0.006	0.01	

1. Analyses based on protocol-specified ANCOVA model with terms for treatment, smoking status at entry, center, and baseline.
2. As per-protocol, data missing due to worsening of COPD are imputed using the worst observation carried forward, otherwise missing data are imputed using LOCF.
Source: Clinical Study Report Appendix, Studies 251 and 252, Tables 15.2.2:1 and 15.2.2:5 (with modifications in format)

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Numerical results for the co-primary efficacy endpoints in the one year studies sub-grouped by gender and age are provided in Table 16. Estimates by race are not provided as approximately 98% of subjects in these studies were white.

Table 16: Co-Primary Efficacy Endpoints by Gender and Age (Pooled One Year Studies)			
FEV1 (chg. from baseline) LS mean (standard error)			
	Placebo	**5µg Spiriva**	**10µg Spiriva**
Male (N=1412)	-0.048 (0.012)	0.084 (0.011)	0.121 (0.011)
Female (N=485)	-0.024 (0.017)	0.099 (0.016)	0.079 (0.016)
Under 65 Years of Age (N=857)	-0.052 (0.016)	0.087 (0.015)	0.109 (0.015)
65 Years of Age and Over (N=1040)	-0.033 (0.012)	0.089 (0.012)	0.109 (0.012)
SGRQ Total Score LS mean (standard error)			
	Placebo	**5µg Spiriva**	**10µg Spiriva**
Male (N=1341)	-1.10 (0.599)	-4.31 (0.571)	-5.19 (0.570)
Female (N=457)	-2.01 (1.197)	-7.49 (1.052)	-7.24 (1.096)
Under 65 Years of Age (N=818)	-2.32 (0.833)	-6.31 (0.757)	-5.44 (0.769)
65 Years of Age and Over (N=980)	-1.15 (0.707)	-4.14 (0.679)	-5.40 (0.682)
TDI Focal Score LS mean (standard error)			
	Placebo	**5µg Spiriva**	**10µg Spiriva**
Male (N=1339)	0.889 (0.139)	1.764 (0.133)	1.772 (0.133)
Female (N=459)	0.522 (0.245)	2.274 (0.216)	2.407 (0.222)
Under 65 Years of Age (N=816)	0.986 (0.192)	2.145 (0.175)	2.191 (0.177)
65 Years of Age and Over (N=982)	0.713 (0.158)	1.632 (0.151)	1.723 (0.152)
Number of COPD Exacerbations Mean rate per patient year			
	Placebo	**5µg Spiriva**	**10µg Spiriva**
Male (N=1476)	1.86	0.81	0.87
Female (N=514)	2.06	1.29	1.46
Under 65 Years of Age	1.53	1.01	0.80
65 Years of Age and Over	2.21	0.87	1.20

Source: Integrated Summary of Efficacy, Table 2.1, 2.3, 2.4, and 2.5 (with modifications in format)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The following statistical issues and their impact have been described in the context of the review. Please refer to the specified section for details.

5.1.1 One Year Studies (254 and 255)

- The **terminology "number of COPD exacerbations"** used to refer to one of the co-primary efficacy endpoints may be slightly misleading in that it actually refers to an incidence rate per year on a subject level. As was indicated in both the protocol and study report and just for clarity is being highlighted here, the number of COPD exacerbations for each subject is expressed per one year of exposure (assuming a constant rate of the event over the time of exposure and/or one year). That is the endpoint is calculated as the number of COPD

exacerbations for a subject divided by the number of days of exposure for the same subject times 365.25 days per year. (Section 3.1.1)

- The protocol defines four co-primary efficacy endpoints. **Co-primary, in this case, is defined in the protocol to indicate that demonstrating a statistically significant difference in favor of treatment with at least one of the endpoints was to be considered adequate demonstration of efficacy.** However, for approval, Division policy would require a benefit in a pulmonary function type measurement, such as trough FEV1 (i.e., improvement in the quality of life measures alone likely would not be adequate for approval). To control the inflation of the type-I error for multiple endpoints, the hypothesis testing for these endpoints was to be conducted sequentially. To control the inflation of the type-I error for multiple doses, for each endpoint a global test of all three treatments was required to be significant before testing each of the doses individually. **This approach is adequate to control the Type I error inflation due to multiple endpoints and multiple doses.** (Section 3.1.1)
- The "full analysis set" (FAS) was defined in the protocol and included all randomized subjects with baseline data and data following at least five days on randomized treatment for at least one primary endpoint. An **additional analysis set was defined for the primary analysis of each co-primary efficacy outcome** (except COPD exacerbations as this was not necessary due to imputation implicit in calculation of this endpoint as previously described). These were each a subset of the FAS but had the **additional requirement that subjects have data for the endpoint of interest following at least five days on randomized treatment.** The inclusion/exclusion of subjects in the SGRQ total score set and TDI focal score set are somewhat imbalanced across treatment groups. This is a potential bias in the results for these endpoints in that the unavailability of a subject's data may be related to the treatment being received; however, in this case it is likely that this bias will **favor the placebo groups** since those who are unavailable after less than five days of treatment are likely those who were dissatisfied with their assigned study treatment and if present would have provided an undesirable score on these quality of life type measures. (Sections 3.1.1 and 3.1.2.1)
- **Missing data for the trough FEV1, SGRQ total score, and TDI focal score**, three of the co-primary efficacy endpoints, resulting from a subject missing post-randomization visit(s) were, according to the protocol, to be imputed with a combination of worst-observation-carried forward and last-observation-carried forward techniques. More subjects in the placebo group relative to that in the Spiriva Respimat groups withdrew early due to worsening COPD. So that the imputation methods could result in potential bias that favors the placebo group since the unobserved data may be worse than what was imputed. However, the **efficacy comparisons appeared to be robust** as various imputations including the observed data alone yielded the same qualitative conclusions. (Sections 3.1.1 and 3.1.2.2)
- Although not explicitly described as a missing data imputation, **missing data for the number of COPD exacerbations** is handled through calculation of the endpoint by assuming that for subjects who prematurely discontinue the study, the rate of the endpoint is the same in the time period the subject was observed

and the remaining portion of the study when the subject was not observed. This could bias the by-treatment group comparisons as generally, more placebo patients discontinue the study early than do active treatment group patients. However, this **bias would likely favor the placebo group** in that those who are dropping out early could be those who are more seriously impaired and/or with deteriorating conditions and thus would have higher event rates after dropping out of the study than before. (Section 3.1.1)

- The **differences between the 5 μg Spiriva Respimat group and placebo and the 10 μg Spiriva Respimat group and placebo were statistically significantly in favor of the Respimat groups for all primary efficacy comparisons** (i.e., for trough FEV1 in both studies, SGRQ total score in both studies, TDI focal score in the pooled analysis of both studies, and number of COPD exacerbations in the pooled analysis of both studies). Although not part of the primary efficacy analysis, note that the difference in the number of COPD exacerbations was statistically significantly in favor of each of the Respimat groups over placebo in study 255 but not in study 254. (Section 3.1.2.2)
- An imbalance in mortality in one of the one-year studies was observed and the sponsor completed an extensive effort to obtain vital status for subjects who withdrew from the studies early. Vital status data is now available for approximately 98% of subjects in all treatment groups so that the possibility of a "healthy survivor effect" being displayed in the placebo group is unlikely. However, **many of the subjects who discontinued early and whose vital status was subsequently determined had been receiving COPD treatment outside of the studies that included the approved Spiriva Handihaler**. If there truly is a mortality effect associated with the use of tiotropium bromide, the mortality rates in the patients who dropped out could be elevated by the use of Spiriva Handihaler. This could **cause a bias in favor of the Spiriva Respimat treatment groups** being that more placebo subjects dropped out than active treatment group subjects. Although analyzing the mortality data without including the retrospective follow-up data might be suggested to mitigate this bias, analyzing the data observed during the course of the study alone is also biased due to the differentially higher dropout of subjects in the placebo groups possibly leading to a "healthy survivor effect". Thus both types of analyses are considered in this document. (Section 3.1.2.3)
- In study 255, the **risk of death in the 10 μg Spiriva Respimat group** was five times as likely as in the placebo group (i.e., the point estimate for the relative risk was 5.0). With 97.5% confidence, we conclude that death for those receiving 10 μg Spiriva Respimat is at least 1.1 times as likely as for those receiving placebo (i.e., the lower limit of the confidence interval for the relative risk is 1.1) and could be as much as 22.9 times as likely (i.e., the upper limit of the confidence interval for the relative risk is 22.9). Analysis of the excess incidence yields similar conclusions indicating with 97.5% confidence that at least two additional deaths and as many as 41 additional deaths should be expected in 1000 patient years of exposure to 10 μg Spiriva Respimat relative to placebo. Study 254 does not confirm these findings but also may not be sufficient to refute them, as demonstrating an effect is not present is an exceedingly difficult task in a clinical study due to limited sample size and variability in observed data. Study 254 is

sufficient to demonstrate, with 97.5% confidence, that the risk of death with 10 µg Spiriva Respimat could be as much as 2.9 times as likely as with placebo and the excess number of deaths in 1000 patient years of exposure to 10 µg Spiriva Respimat relative to placebo could reach 21. (Section 3.1.2.3)

- **Mortality for the 5 µg Spiriva Respimat group** is not statistically significantly different from that of placebo in study 254. In study 255, there is no statistically significant difference in mortality in the 5 µg Spiriva Respimat group relative to placebo; however, the confidence intervals for the differences between treatments are shifted towards the region favoring placebo. Thus although not statistically significantly different from placebo, these results may not be sufficient to rule out a mortality effect, given the effect seen with the higher dose. (Section 3.1.2.3)

5.1.2 Twelve Week Studies (251 and 252)

- A **sequence of hypothesis testing** was used to first test the superiority of each Spiriva dose over placebo, then the noninferiority of each dose of Spiriva to ipratropium bromide, and finally the superiority of each dose of Spiriva to ipratropium bromide. This approach **adequately controlled the Type I error rate**. (Section 3.2.1)
- **Missing data** resulting from a subject missing post-randomization visit(s) were, according to the protocol, to be imputed with a combination of worst-observation-carried forward and last-observation-carried forward techniques. **Efficacy comparisons appeared to be robust** to these imputations as the observed data alone yielded the same qualitative conclusions as that of the data with imputation. (Section 3.2.1 and 3.2.2.2)
- Both the **5 µg Spiriva Respimat group and 10 µg Spiriva Respimat group were statistically significantly superior to placebo in terms of the primary efficacy endpoint**, trough FEV1, in both studies. Both the **5 µg Spiriva Respimat group and 10 µg Spiriva Respimat group were noninferior to Ipratropium bromide in terms of the primary efficacy endpoint**, trough FEV1, in both studies. The **10 µg Spiriva Respimat group was statistically significantly superior to Ipratropium Bromide in terms of the primary efficacy endpoint**, trough FEV1, in both studies. The **5 µg Spiriva Respimat group was statistically significantly superior to Ipratropium Bromide in terms of the primary efficacy endpoint**, trough FEV1, in study 252 but not in study 251. (Section 3.2.2.2)

5.2 Conclusions and Recommendations

In the one-year studies, studies 254 and 255, in patients with chronic obstructive pulmonary disease (COPD), the 5 µg Spiriva Respimat and 10 µg Spiriva Respimat groups each had statistically significant better average outcomes in terms of the four co-primary efficacy endpoints (trough FEV1 in each study, SGRQ total score in each study, TDI focal score in the prespecified pooled analysis of both studies, and number of COPD exacerbations in the prespecified pooled analysis of both studies) than the

placebo group. The efficacy conclusions are robust against concerns regarding missing data as analysis of the observed data only yielded supportive conclusions.

In study 255, the risk of death was statistically significantly higher in the 10 μg Spiriva Respimat group than the placebo group. Study 254 does not confirm these findings but also may not be sufficient to refute them, as demonstrating an effect is not present is an exceedingly difficult task in a clinical study due to limited sample size and variability in observed data. Mortality for the 5 μg Spiriva Respimat group is not statistically significantly different from that of placebo in study 254. In study 255, there is no statistically significant difference in mortality in the 5 μg Spiriva Respimat group relative to placebo; however, the confidence interval for the differences between treatments is shifted towards the region favoring placebo. Thus although not statistically significantly different from placebo, these results may not be sufficient to rule out a mortality effect, given the effect seen with the higher dose.

In both of the 12-week studies, studies 251 and 252, in patients with COPD, the 5 μg Spiriva Respimat and 10 μg Spiriva Respimat groups each had statistically significant better average trough FEV1 at 12-weeks than the placebo groups. In addition, in both of the 12-week studies, the 5 μg Spiriva Respimat and 10 μg Spiriva Respimat were each demonstrated to be noninferior to Ipratropium in terms of average trough FEV1 at 12 weeks (with a noninferiority margin of -0.05). Finally, the 10 μg Spiriva Respimat group was statistically significantly superior to Ipratropium in both of the 12-week studies while the 5 μg Spiriva Respimat group was significantly superior to Ipratropium in study 252 but not study 251. The efficacy conclusions are robust against concerns regarding missing data as analysis of the observed data only yielded supportive conclusions.

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