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 207070
Drug Name:	Spiriva Respimat (Tiotropium Bromide) Inhalation Spray
Indication(s):	Long-term, once daily, add-on maintenance treatment of asthma in patients who remain symptomatic on at least inhaled corticosteroids
Applicant:	Boehringer Ingelheim
Date(s):	Receipt date: August 15, 2014
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Biometrics Division:	Division of Biometrics II
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Keywords: NDA, clinical studies

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1 EXECUTIVE SUMMARY

Spiriva Respimat (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. Spiriva Respimat (tiotropium) inhalation spray for the maintenance of airflow and for reducing exacerbations in patients with COPD was approved September 24, 2014. BI proposes Spiriva Respimat (tiotropium bromide) inhalation spray for the long-term, once daily, add-on maintenance treatment of asthma inpatients 12 years of age and older who remain symptomatic on at least inhaled corticosteroids.

There were 7 phase 3 (205.416, 205.417, 205.418, 205.419, 205.442, 205.444, and 205.456), double-blind, placebo-controlled efficacy and safety studies of Spiriva Respimat added on top of usual background medication in patients with asthma who were not optimally controlled with their current asthma treatment. The analysis pooled data from the two 52-week exacerbation trials, studies 205.416 and 205.417, showed a significant improvement for the primary endpoint, time to first severe asthma exacerbation, after 48 weeks of treatment with Spiriva Respimat 5 mcg. There was a 21% reduction in the risk of having a severe asthma exacerbation in a year for Spiriva Respimat over placebo. However, as the pooled analysis is considered as one study, the applicant did not provide replicated evidence of an exacerbation benefit. Regardless, both studies 205.416 and 205.417 demonstrated a statistically significant treatment effect in favor of Spiriva Respimat 5 mcg over placebo for the first two primary endpoints FEV_1 $peak_{0\text{-}3h}$ and trough FEV_1 at 24 weeks. Both studies 205.418 and 205.419 demonstrated a statistically significant treatment effect in favor of both Spiriva Respimat 5 mcg and 2.5 mcg over placebo for the first two primary endpoints FEV_1 $peak_{0\text{-}3h}$ and trough FEV_1 at 24 weeks. Study 205.442 also demonstrated a statistically significant treatment effect of both Spiriva Respimat 5 mcg and 2.5 mcg over placebo for the primary endpoint FEV_1 $peak_{0\text{-}3h}$ and the key secondary endpoint trough FEV_1 at 24 weeks. There were no pre-specified multiplicity corrections in place for any of the secondary endpoints. There were two adolescent studies, 205.444 and 205.456. Only study 205.444 demonstrated a statistically significant treatment effect in both Spiriva Respimat 5 mcg and 2.5 mcg over placebo for the primary endpoint FEV_1 $peak_{0\text{-}3h}$. The secondary endpoint, trough FEV_1 for study 205.444 only demonstrated a statistically significant treatment effect in the Spiriva Respimat 5 mcg over placebo, but not Spiriva Respimat 2.5 mcg. There was not a statistically significant treatment effect for the secondary endpoint, time to first severe asthma exacerbation for either Spiriva Respimat dose over placebo in study 205.444.

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Spiriva Respimat (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. BI proposes Spiriva Respimat 2.5 (b) (4) for the long-term, once daily, add-on maintenance treatment of asthma in patients 12 years of age and older who remain symptomatic on at least inhaled corticosteroids. However, the Division of Pulmonary, Allergy, and Rheumatology Products proposes Spiriva Respimat be approved at a dose of 2.5 mcg. (b) (4) .

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 communications and interactions relevant to statistical review are summarized herein.

There was a Type B End-of-Phase 2 meeting held on June 9, 2008 to discuss the proposed phase 3 studies and development plan for Spiriva Respimat for the treatment of asthma. (b) (4) BI requested comments on a planned interim analysis. The Division responded an interim analysis for sample size adjustment is reasonable given their results was replicated.

(b) (4)

2.1.3 Specific Studies Reviewed

This review will focus on the results from studies 205.416 and 205.417 (hereafter referred to as 416 and 417, respectively). The results from the studies 205.418, 205.419, 205.442, 205.444, and 205.456 (hereafter referred to as 418, 419, 442, 444, and 456 respectively) will be used to support Spiriva Respimat 2.5 mcg.

2.2 Data Sources

The submission of NDA 207070 was submitted on August 15, 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\NDA207070\0000.

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 the efficacy studies are shown in Table 1. Each study is discussed below.

Table 1: Summary of Study Design and Primary Endpoints

Study ID	Length of the Study	Treatment Arms*	Number of Patients	Study Population	Primary Efficacy Endpoint(s)
416	48 weeks DB period	SR 5 mcg Placebo	237 222	Severe persistent asthma	Peak FEV_1 0-3 hours after 24 weeks Trough FEV_1 after 24 weeks Time to first severe exacerbation at 48 weeks
417	48 weeks DB period	SR 5 mcg Placebo	219 234	Severe persistent asthma	Peak FEV_1 0-3 hours after 24 weeks Trough FEV_1 after 24 weeks Time to first severe exacerbation at 48 weeks
418	24 weeks DB period	SR 2.5 mcg SR 5 mcg Salmeterol 50 mcg Placebo	262 265 275 269	Moderate persistent asthma	Peak FEV_1 0-3 hours after 24 weeks Trough FEV_1 after 24 weeks
419	24 weeks DB period	SR 2.5 mcg SR 5 mcg Salmeterol 50 mcg Placebo	258 254 266 259	Moderate persistent asthma	Peak FEV_1 0-3 hours after 24 weeks Trough FEV_1 after 24 weeks
442	12 weeks DB	SR 2.5 mcg SR 5 mcg Placebo	154 155 156	Mild persistent asthma	Peak FEV_1 0-3 hours after 12 weeks
444	48weeks DB	SR 2.5 mcg SR 5 mcg Placebo	125 135 138	Moderate persistent asthma	Peak FEV_1 0-3 hours after 24 weeks
456	12 weeks DB	SR 2.5 mcg SR 5 mcg Placebo	127 130 135	Severe persistent asthma	Peak FEV_1 0-3 hours after 12 weeks

Source: Reviewer
* SR = Spiriva Respimat, DB: double blind

3.2.1.1 Studies 416 and 417

Studies 416 and 417 were phase 3, randomized, double-blind, parallel-group, placebo-controlled, multi-center, multi-national 48 week studies. These studies where designed to evaluate the efficacy and safety of tiotropium inhalation solution 5 mcg (2 puffs of 2.5 mcg) administered once daily in the morning via the Respimat inhaler in patients with severe persistent asthma as add-on therapy. The study medication was added on top of the usual background medication in patients that were not optimally controlled with their current asthma treatment. Usual background medication included (at a minimum) high-dose inhaled corticosteroids (ICS) and long-acting β2-adrenergic agonists (LABAs). Salbutamol (also known as albuterol), a short-acting β2-adrenergic agonist (SABA), was provided (at visit 0) as rescue medication for use as necessary during the study.

Both studies contained three primary endpoints. The first two, change from baseline in maximum FEV_1 measured within the first 3 hours after study drug administration (FEV_1 $peak_{0-3h}$) and change from baseline in trough FEV_1 both were measured at 24 weeks. The third primary endpoint, time to first severe asthma exacerbation after 48 weeks of treatment, was considered

primary only in the analysis of the pooled data from studies 416 and 417. 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. An asthma exacerbation (including severe, non-severe; symptomatic, asymptomatic; i.e. any exacerbation) was defined as an episode of progressive increase in 1 or more asthma symptoms (e.g. shortness of breath, cough, wheezing, or chest tightness, or some combination of these symptoms). The symptoms should be outside the patient's usual range of day-to-day asthma symptoms and must persist for at least two consecutive days. A severe asthma exacerbation was defined as an asthma exacerbation that required treatment with systemic (including oral) corticosteroids for at least three days or in case of ongoing and pre-existing systemic corticosteroids therapy that required at least a doubling of the previous daily dose of systemic corticosteroids for at least three days. Severe exacerbations that required courses of systemic corticosteroids separated by 1 week or more were treated as separate events. Symptomatic asthma exacerbations were defined as the subgroup of asthma exacerbations that resulted in asthma symptoms with or without a decrease in peak expiratory flow (PEF). Thus, exacerbations without symptoms (i.e. PEF decreases only) were not included in this category. This definition was implemented post-hoc.

3.2.1.2 Studies 418 and 419

Studies 418 and 419 were phase 3, randomized, double-blind, double-dummy, active- and placebo-controlled, parallel-group 24 week studies. The studies where designed to evaluate the efficacy and safety of two doses of tiotropium inhalation solution via the Respimat inhaler, 5 mcg (2 puffs of 2.5 mcg) and 2.5 mcg (2 puffs of 1.25 mcg), compared to placebo and to salmeterol 50 mcg via the metered dose inhaler (MDI) on top of add-on therapy in patients with moderate, persistent asthma. Patients received either 5 mcg of Spiriva Respimat, 2.5 mcg of Spiriva Respimat, 50 mcg of salmeterol or placebo (tiotropium matching placebo administered via the Respimat inhaler and salmeterol matching placebo administered via the MDI). The patients inhaled 2 puffs from the MDI (salmeterol or placebo) every morning and every evening, and 2 puffs from the Respimat inhaler (Spiriva Respimat or placebo) every evening. The usual background medication included medium-dose ICS, alone or with fixed combination with a LABA or SABA. Salbutamol was provided as a rescue medication for use as necessary during the study.

Both studies contained three primary endpoints. The first two, change from baseline in maximum FEV_1 measured within the first 3 hours after study drug administration (FEV_1 $peak_{0\text{-}3h}$) and change from baseline in trough FEV_1 both were measured at 24 weeks. 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 third primary endpoint, the responder rate as assessed by the Asthma Control Questionnaire (ACQ) at the end of the 24-week treatment period, was considered primary only in the analysis of the pooled data from studies 418 and 419. The ACQ response was calculated as the mean of the responses to all 7 questions in the ACQ.

3.2.1.3 Study 442

Study 442 was a phase 3, multi-center, multi-national, randomized, double-blind, placebo-controlled, parallel-group 12 week study. This study was designed to evaluate the

efficacy and safety of two doses of Spiriva Respimat 5 mcg (2 puffs of 2.5 mcg) and 2.5 mcg (2 puffs of 1.25 mcg) compared to placebo on top of add-on therapy in patients with mild, persistent asthma. The patients were to inhale Spiriva Respimat or placebo once daily in the evening. The usual background medication included low-dose ICS, alone or with fixed combination with a SABA. Those patients who were taking fixed combination ICS and SABA were to stop taking the fixed combination product and switch to the ICS mono-product at least 8 hours prior to visit 1. Salbutamol was provided as a rescue medication for use as necessary during the study.

The primary efficacy endpoint was change from baseline in maximum FEV_1 measured within the first 3 hours after study drug administration (FEV_1 $peak_{0-3h}$) at the end of the 12 week treatment. The key secondary endpoint was trough FEV_1 at the end of 12 weeks. The baseline FEV_1 was defined as the pretreatment FEV_1 measurement at visit 2 in the evening 10 minutes prior to the first dose of the randomization treatment.

3.2.1.4 Study 444

Study 444 was a phase 3, multi-center, multi-national, randomized, double-blind, placebo-controlled, parallel-group 48 week study. This study was designed to evaluate the efficacy and safety of two doses of Spiriva Respimat 5 mcg (2 puffs of 2.5 mcg) and 2.5 mcg (2 puffs of 1.25 mcg) compared to placebo on top of add-on therapy in adolescent patients (12 to 17 years) with moderate, persistent asthma. The patients were to inhale Spiriva Respimat or placebo once daily in the evening. The usual background medication included medium-dose ICS, alone or with fixed combination with a LABA or a leukotriene modifier (LTRA). Those patients who were taking fixed combination ICS and LABA were switched to the ICS mono-product without changing the steroid dose prior to visit 1. LTRA was permitted throughout the study; however, the LABA had to be stopped at least 72 hours prior to visit 1. Salbutamol was provided as a rescue medication for use as necessary during the study.

The primary efficacy endpoint was change from baseline in maximum FEV_1 measured within the first 3 hours after study drug administration (FEV_1 $peak_{0-3h}$) at the end of the 24 weeks of the treatment. The secondary endpoint was trough FEV_1 at the end of 24 weeks of the treatment. The baseline FEV_1 was defined as the pretreatment FEV_1 measurement at visit 2 in the evening 10 minutes prior to the first dose of the randomization treatment.

3.2.1.5 Study 456

Study 456 was a phase 3, multi-center, multi-national, randomized, double-blind, placebo-controlled, parallel-group, 12 week study. This study was designed to evaluate the efficacy and safety of two doses of Spiriva Respimat 5 mcg (2 puffs of 2.5 mcg) and 2.5 mcg (2 puffs of 1.25 mcg) compared to placebo on top of add-on therapy in adolescent patients (12 to 17 years) with severe, persistent asthma. The patients were to inhale Spiriva Respimat or placebo once daily in the evening. The usual background medication included high-dose ICS, in combination with at least one controller medication such as a LABA or a LTRA or at stable medium dose in combination with two or more other controller medications such as a LABA and/or a LTRA and/or a sustained release theophylline for at least four weeks before screening. Salbutamol was provided as a rescue medication for use as necessary during the study.

The primary efficacy endpoint was change from baseline in FEV_1 $peak_{0\text{-}3h}$ at the end of the 12 weeks of the treatment. The key secondary endpoint was trough FEV_1 at the end of 12 weeks of treatment. Baseline FEV_1 was defined as the pretreatment FEV_1 measurement at visit 2 in the evening 10 minutes prior to the first dose of the randomization treatment.

3.2.2 Statistical Methodologies

All efficacy analyses were performed using the full analysis set (FAS), which was defined as all randomized patients who received at least one dose of the study medication and had at least one on-treatment efficacy measurement. Missing FEV_1 data was replaced with the least favorable FEV_1 value if a patient withdrew due to worsening of asthma. This is analogous to worst observation carried forward. Missing baseline data was not imputed. Data obtained after the intake of rescue medication was considered missing. Missing observations that had data from visits both before and after were linearly interpolated; baseline value was used if necessary. This applied to multiple consecutive missing values as well. The last observation carried forward (LOCF) method was used if there were missing observations after the missing visit of interest. The Division generally does not accept LOCF as an imputation strategy as it may assign a positive outcome to a patient who showed early FEV_1 improvement but could not tolerate or adhere to the therapy long term. The use of least favorable value addresses this concern.

3.2.2.1 Studies 416 and 417

There were two sites included in the FAS where the patients were non-compliant, sites 49003 and 07002. The protocol pre-specified that in both studies the first two primary endpoints change from baseline in FEV_1 $peak_{0\text{-}3h}$ and trough FEV_1 after 24 weeks, were analyzed using a restricted maximum likelihood (REML)-based repeated measures approach with fixed effects of center, visit, treatment, treatment-by-visit interaction, baseline and baseline-by-visit interaction. The third primary endpoint time to first severe asthma exacerbation after 48 weeks was conducted by pooling studies 416 and 417 and was analyzed using a Cox's proportional hazards regression model with treatment fitted as an effect. Only severe asthma exacerbations with onset during randomized treatment were included in the analysis. For all three primary endpoints a stepwise manner was used to protect the overall type I error. If superiority of Spiriva Respimat over placebo was established for FEV_1 $peak_{0\text{-}3h}$ at the 2.5% level (one-sided) then the treatment groups were compared for change in baseline in trough FEV_1. If superiority of Spiriva Respimat over placebo was established for trough FEV_1 at the 2.5% level (one-sided) then the treatment groups were compared for the time to first severe asthma exacerbation using the pooled data at the 5% level (two-sided). Note, missing data was low (7% in study 416 and 6% in study 417) and was not a concern.

The protocol pre-specified an interim analysis to re-adjust the sample size based on the observed hazard ratio of severe asthma exacerbations at the interim analysis. The interim analysis was performed once the total number of patients with at least 1 severe asthma exacerbation in the two studies (416 and 417) together reached 65. This analysis was conducted by an independent Data Monitoring Committee (IDMC), which only received unblinded exacerbation data. The IDMC could have either recommended to limit the recruitment of patients to 150 per treatment group in

each study or to increase the sample size to 200 per treatment group in each study based on what was observed in the interim analysis. The IDMC recommended increasing the sample size to 200 patients per treatment group in each study. As pre-specified in the statistical analysis, the p-value for the third primary endpoint time to first severe asthma exacerbation from the pooled data was adjusted for the unblinded interim analysis. The adjusted p-value using the weighted test statistic was calculated as below:

$$Z = \frac{\omega_1 Z_1 + \omega_2 Z_2}{\sqrt{\omega_1{}^2 + \omega_2{}^2}} \quad (\sim N(0,1)),$$

where

(i) $Z_1 = \sqrt{T_1}$ $(\sim N(0,1))$, and T_1 is the Wald test statistic at the interim time point

(ii) $$Z_2 = \frac{\sqrt{d_t} * Z_t - \sqrt{d_1} * Z_1}{\sqrt{d_2}} \ (\sim N(0,1))$$

a. d_1 is the number of observed events at interim time point, d_t is the total number of events observed during the entire trial and $d_2 = d_t - d_1$

b. $Z_t = \sqrt{T_t}$ $(\sim N(0,1))$, and T_t is the Wald test statistic for the entire trial

(iii) The weights ω_1 and ω_2 need be chosen so, that $\omega_1{}^2 + \omega_2{}^2 = 1$. According the CTP, the number of events at interim time point and after interim time point are expected to be approximately equal (65 in period 1 and 61 in period 2), therefore we chose $\omega_1 = \omega_2 = \sqrt{\frac{1}{2}}$.

In this case the applicant had for the events the following numbers: $d_1 = 74$ number of observed events at interim time point and $d_t = 271$ total number of events observed during the entire study.

The p-value can be calculated using probnorm (Z) in SAS as

p = probnorm (Z) if Z<0
p = 1- probnorm (Z) if Z≥0

The applicant decided post-hoc to analyze the FEV_1 endpoints using the increased sample size even though the interim analysis was based on the exacerbation endpoint. They did not adjust the p-value for the interim analysis for the FEV_1 endpoints.

3.2.2.2 Studies 418 and 419

The protocol pre-specified that in both studies the first two primary endpoints change from baseline in FEV_1 $peak_{0\text{-}3h}$ and trough FEV_1 after 24 weeks were analyzed using a REML-based MMRM approach with fixed effects of center, visit, treatment, treatment-by-visit interaction,

baseline and baseline-by-visit interaction. ACQ responder was analyzed using Fisher's Exact Test. Patients were considered responders if they had an improvement (decrease) in ACQ total score of at least 0.5 points, which is the minimal important difference compared to baseline.

For the three primary endpoints a stepwise approach was used to protect the overall type I error. The 5 mcg dose was tested first. If all three primary endpoints were significantly different from placebo at the 2.5% level for the 5 mcg dose, then the 2.5 mcg dose was tested at the 2.5% level. Missing data was low (1% for study 418 and 6% for study 419) for both studies 418 and 419.

3.2.2.3 Study 442

The primary endpoint, change from baseline in FEV_1 $peak_{0\text{-}3h}$ after 12 weeks, was analyzed using a REML-based mixed effects model with MMRM. The model included fixed effects of center, visit, treatment, treatment-by-visit interaction, and covariates of baseline FEV_1 $peak_{0\text{-}3h}$ and baseline-by-visit interaction. The key secondary endpoint, trough FEV_1 after 12 weeks, was analyzed similar to the primary endpoint. A stepwise manner was used to protect the overall type I error for only the primary endpoint. The 5 mcg dose was tested first. If the primary endpoint was significantly different from placebo at the 2.5% level for the 5 mcg dose, then the 2.5 mcg dose was tested at the 2.5% level. Missing data was low (2%) for study 442.

3.2.2.4 Study 444

Change from baseline in FEV_1 $peak_{0\text{-}3h}$ after 24weeks was analyzed using a REML-based mixed effects model with MMRM. The model included fixed effects of center, visit, treatment, treatment-by-visit interaction, and covariates of baseline FEV_1 $peak_{0\text{-}3h}$ and baseline-by-visit interaction. Trough FEV_1, after 24 weeks was analyzed similar to the primary endpoint. A stepwise manner was used to protect the overall type I error for the primary endpoint. The 5 mcg dose was tested first. If the endpoint was significantly different from placebo at the 2.5% level for the 5 mcg dose, then the 2.5 mcg dose was tested at the 2.5% level. There was no multiplicity adjustment for any of the secondary endpoints, including trough FEV_1. Missing data was low (5%) for study 444.

3.2.2.5 Study 456

The primary endpoint, change from baseline in FEV_1 $peak_{0\text{-}3h}$ after 12 weeks was analyzed using a REML-based mixed effects model with MMRM. The model included fixed effects of country, visit, treatment, treatment-by-visit interaction, and covariates of baseline FEV_1 $peak_{0\text{-}3h}$ and baseline-by-visit interaction. The key secondary endpoint trough FEV_1 after 12 weeks was analyzed similar to the primary endpoint. A stepwise manner was used to protect the overall type I error. The 5 mcg dose was tested first for the primary endpoint. If the primary endpoint was significantly different from placebo at the 2.5% level for the 5 mcg dose, then the 2.5 mcg dose was tested at the 2.5% level. This sequence was then repeated for the key secondary endpoint. Missing data was low (2%) for study 456.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Study 416 and 417

The summary of the patient disposition for the treated set (TS) in studies 416 and 417 are given in Table 2. The treated set was defined as all randomize patients who were received at least 1 dose of randomized study medication. Approximately 10%-11% of the patients discontinued study medication in both studies over 48 weeks. Note that only 6%-7% of the patients discontinued the study medication by 24 weeks. The primary reason for discontinuation in both groups was adverse advents (AE). Protocol violations accounted for about 6% overall for the discontinuations in both studies.

Table 2 Summary of Patient Disposition in Studies 416 and 417 (48 weeks)

	Study 416		Study 417	
	Spiriva Respimat n (%)	Placebo n (%)	Spiriva Respimat n (%)	Placebo n (%)
Randomized	237	222	219	234
TS	237 (100)	222 (100)	219 (100)	234 (100)
FAS	237 (100)	222 (100)	216 (99)	232 (99)
Completed	211 (89)	202 (91)	198 (90)	203 (87)
Discontinued	26 (11)	20 (9)	21 (10)	31 (13)
Adverse Event	6 (3)	6 (3)	2 (1)	8 (3)
Worsening of disease under study	2 (0.8)	3 (1)	1 (0.5)	5 (2)
Worsening of other pre-existing disease	0	0	0	0
Lack of Efficacy	1 (0.4)	0	1 (0.5)	0
Non-compliant with protocol	3 (1)	3 (1)	2 (1)	0
Lost to Follow-up	1 (0.4)	1 (0.5)	0	2 (1)
Refused to continue taking trial medication	8 (3)	3 (1)	7 (3)	12 (5)
Other	7 (3)	7 (3)	9 (4)	5 (2)

Source: Reviewer Analysis

The patients' mean age was about 53 years. Most of the patients were White (82%-84%) in these studies. These factors were generally well-balanced across the treatment groups. The summary of the demographics is given in Table 3.

Table 3 Demographics in Studies 416 and 417- Treated Set

	Study 416		Study 417	
	Spiriva Respimat N=237	Placebo N=222	Spiriva Respimat N=219	Placebo N=234
Age (years) Mean (SD)	53 (12)	54 (13)	51 (13)	54 (12)
Sex n (%)				
Female	146 (62)	143 (64)	127 (58)	135 (58)
Male	91 (38)	79 (36)	92 (42)	99 (42)
Race n (%)				
White	200 (84)	187 (84)	176 (80)	196 (84)
Black/ African American	9 (3.8)	11 (5)	13 (6)	14 (6)
Asian	27 (11)	23 (10)	29 (13)	24 (10)
Native Hawaiian/Pac Islander	0	1 (1)	1 (1)	0
American Indian/Alaska Native	1 (<1)	0	0	0
Height (cm) Mean (SD)	167 (10)	166 (10)	167 (10)	167 (11)
Weight (kg) Mean (SD)	79 (18)	78 (20)	79 (18)	79 (19)
Smoking History, N (%)				
Never smoked	182 (77)	174 (78)	158 (72)	178 (76)
Ex-smoker	55 (23)	48 (22)	61 (28)	56 (24)
Mean pack years (SD)	6 (3)	5 (3)	5 (3)	5 (3)

Source: Reviewer Analysis

3.2.3.2 Studies 418 and 419

The summary of the patient disposition in study 418 and study 419 are given in Table 4 and Table 5, respectively. Approximately 5% to 6% of the patients withdrew from treatment in both studies. The primary reason for discontinuation in each treatment group for study 418 was listed as other. Approximately 2% of the patients discontinued study 418 due to AEs, 3% in the placebo and Spiriva 5 mcg groups, 2% in the Spiriva Respimat 2.5 mcg group, and 1 % in Salmeterol group. In study 419, the primary reason for discontinuation was AEs with 5% (2 patients in Spiriva Respimat 2.5mcg, 2 patients in Spiriva Respimat 5 mcg, 7 patients in Salmeterol, and 5 patients in placebo).

Table 4 Summary of Patient Disposition in Study 418

	Spiriva Respimat 2.5mcg N (%)	Spiriva Respimat 5mcg N (%)	Salmeterol N (%)	Placebo N (%)
Randomized	262	265	275	269
TS	262 (100)	264 (100)	275 (100)	269 (100)
FAS	259 (99)	261 (99)	271 (99)	265 (99)
Completed	249 (95)	241 (91)	260 (95)	248 (92)
Discontinued	13 (5)	23 (9)	15 (6)	21 (8)
Adverse Event	4 (2)	8 (3)	3 (1)	8 (3)
Worsening of disease under study	0	3 (1)	1 (<1)	4 (2)
Worsening of other pre-existing disease	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Other AE	3 (1)	4 (2)	1 (<1)	3 (1)
Lack of Efficacy	0	0	0	1 (<1)
Non-compliant with protocol	2 (1)	2 (1)	0	2 (1)
Lost to Follow-up	1 (<1)	1 (<1)	3 (1)	0
Consent withdrawn (not due to AE)	1 (<1)	3 (1)	2 (1)	4 (2)
Other	5 (2)	9 (3)	7 (3)	6 (2)

Source: Reviewer Analysis

Table 5 Summary of Patient Disposition in Study 419

	Spiriva Respimat 2.5mcg N (%)	Spiriva Respimat 5mcg N (%)	Salmeterol N (%)	Placebo N (%)
Randomized	258	254	266	259
TS	257 (100)	253 (100)	266 (100)	254 (100)
FAS	256 (99)	252 (99)	264 (99)	253 (99)
Completed	245 (95)	240 (95)	249 (94)	240 (95)
Discontinued	12 (5)	13 (5)	17 (6)	14 (6)
Adverse Event	2 (1)	2 (1)	7 (3)	5 (2)
Worsening of disease under study	1 (<1)	0	3 (1)	3 (1)
Worsening of other pre-existing disease	0	0	1 (<1)	0
Other AE	1 (<1)	2 (1)	3 (1)	2 (1)
Lack of Efficacy	0	0	0	0
Non-compliant with protocol	2 (1)	1 (<1)	2 (1)	0
Lost to Follow-Up	1 (<1)	2 (1)	2 (1)	4 (2)
Consent withdrawn (not due to AE)	3 (1)	3 (1)	3 (1)	2 (1)
Other	4 (2)	5 (2)	3 (1)	3 (1)

Source: Reviewer Analysis

Demographics and baseline characteristics for all randomized and treated patients in studies 418 and 419 are summarized in Tables 6 and 7, respectively. The patients' mean age was about 43 years in both studies. Forty-eight percent of the patients were White in study 418 and 47% in study 419. These factors were generally well-balanced across the treatment groups in both studies.

Table 6 Demographics in Study 418- Treated Set

	Spiriva Respimat 2.5mcg N=262	Spiriva Respimat 5mcg N=264	Salmeterol N=275	Placebo N=269
Age (years)				
Mean (SD)	44 (13)	44 (13)	43 (13)	43 (13)
Sex n (%)				
Female	156 (60)	154 (58)	159 (58)	166 (62)
Male	106 (41)	110 (42)	116 (42)	103 (38)
Race n (%)				
White	130 (50)	121 (46)	139 (51)	128 (48)
Black/ African American	7 (3)	13 (5)	7 (3)	14 (5)
Asian	110 (42)	116 (44)	115 (42)	111 (41)
Native Hawaiian/Pac Islander	0	0	0	1
American Indian/Alaska Native	15 (6)	14 (5)	14 (5)	14 (5)
Height (cm)				
Mean (SD)	165 (10)	165 (10)	166 (10)	165 (10)
Weight (kg)				
Mean (SD)	73 (18)	74 (18)	74 (19)	73 (19)
Smoking History, N (%)				
Never smoked	224 (86)	225 (85)	233 (85)	241 (90)
Ex-smoker	38 (15)	39 (15)	42 (15)	28 (10)
Mean pack years (SD)	4 (3)	4 (3)	4 (3)	5 (3)

Source: Reviewer Analysis

Table 7 Demographics in Study 419- Treated Set

	Spiriva Respimat 2.5mcg N=257	Spiriva Respimat 5mcg N=253	Salmeterol N=266	Placebo N=254
Age (years)				
Mean (SD)	43 (13)	44 (13)	41 (13)	43 (13)
Sex n (%)				
Female	160 (62)	146 (58)	153 (58)	145 (57)
Male	97 (37)	107 (42)	113 (43)	109 (43)
Race n (%)				
White	123 (48)	119 (47)	127 (48)	118 (47)
Black/ African American	10 (4)	9 (4)	8 (3)	13 (5)
Asian	110 (43)	109 (43)	114 (43)	108 (43)
Native Hawaiian/Pac Islander	2 (1)	0	0	0
American Indian/Alaska Native	12 (5)	16 (6)	17 (6)	15 (6)
Height (cm)				
Mean (SD)	166 (10)	166 (9)	166 (9)	166 (10)
Weight (kg)				
Mean (SD)	73 (20)	75 (19)	74 (20)	75 (20)
Smoking History, N (%)				
Never smoked	213 (83)	195 (77)	213 (80)	212 (84)
Ex-smoker	44 (17)	58 (23)	53 (20)	42 (17)
Mean pack years (SD)	4 (3)	5 (3)	4 (3)	4 (3)

Source: Reviewer Analysis

3.2.3.3 Study 442

The summary of the patient disposition in study 442 is given in Table 8. Approximately 2% of the patients withdrew from the study medication. The primary reason for discontinuations of the study medication was AE and consent withdrawn, both with 1%.

Table 8 Disposition in Study 442

	Spiriva Respimat 2.5 mcg N (%)	Spiriva Respimat 5 mcg N (%)	Placebo N (%)
Randomized	154	155	156
TS	154 (100)	155 (100)	155 (99)
FAS	154 (100)	155 (100)	155 (99)
Completed	149 (97)	152 (98)	154 (99)
Discontinued	5 (3)	3 (2)	1 (1)
Adverse Event	2 (1)	1 (1)	0
Worsening of disease under study	2 (1)	0	0
Worsening of other pre-existing disease	0	0	0
Other AE	0	1 (1)	0
Lack of Efficacy	0	0	0
Non-compliant with protocol	0	1 (1)	0
Lost to Follow-Up	0	0	0
Consent withdrawn (not due to AE)	2 (1)	0	1 (1)
Other	1 (1)	1 (1)	0

Source: Reviewer Analysis

The demographics and baseline characteristics in study 442 are summarized for the TS population in Table 9. The patients' mean age was about 43 years. Seventy-eight percent of the patients were White with 61% of the patients being. These factors were generally well-balanced across the treatment groups.

Table 9 Demographics in Study 442- Treated Set

	Spiriva Respimat 2.5 mcg N=154	Spiriva Respimat 5 mcg N=155	Placebo N=155
Age (years)			
Mean (SD)	44 (14)	42 (13)	43 (12)
Sex n (%)			
Female	82 (53)	103 (67)	96 (62)
Male	72 (47)	59 (38)	52 (34)
Race n (%)			
White	121 (79)	122 (79)	119 (77)
Black/ African American	0	0	1 (1)
Asian	26 (17)	29 (19)	30 (19)
American Indian/Alaska Native	7 (5)	4 (3)	5 (3)
Height (cm)			
Mean (SD)	168 (11)	167 (10)	167 (10)
Weight (kg)			
Mean (SD)	74 (17)	75 (17)	73 (17)
Smoking History, N (%)			
Never smoked	131 (85)	122 (79)	129 (83)
Ex-smoker	23 (15)	33 (21)	26 (17)
Mean pack years (SD)	4 (3)	4 (3)	6 (3)

Source: Reviewer Analysis

3.2.3.4 Study 444

The summary of the patient disposition in study 444 is given in Table 10. Approximately 5% of the patients withdrew from the study medication. The primary reason for discontinuation overall was other with 2%, 4%, 2%, and 1% in the Spiriva Respimat 2.5 mcg, 5 mcg, and placebo, respectively.

Table 10 Disposition in Study 444

	Spiriva Respimat 2.5 mcg N (%)	Spiriva Respimat 5 mcg N (%)	Placebo N (%)
Randomized	125	135	138
TS	125 (100)	134 (99)	138 (99)
FAS	125 (100)	134 (99)	138 (100)
Completed	115 (92)	129 (96)	132 (96)
Discontinued	10 (8)	5 (4)	6 (4)
Adverse Event	0	0	2 (1)
Worsening of disease under study	0	0	2 (1)
Worsening of other pre-existing disease	0	0	0
Other AE	0	0	0
Lack of Efficacy	1 (1)	0	0
Non-compliant with protocol	0	1 (1)	3 (2)
Lost to Follow-Up	0	0	0
Consent withdrawn (not due to AE)	4 (3)	1 (1)	0
Other	5 (4)	3 (2)	1 (1)

Source: Reviewer Analysis

The demographics and baseline characteristics in study 444 are summarized for the TS population in Table 11. The patients' mean age was about 14 years. Most of the patients were White (93%). These factors were generally well-balanced across the treatment groups.

Table 11 Demographics in Study 444- Treated Set

	Spiriva Respimat 2.5 mcg N=125	Spiriva Respimat 5 mcg N=134	Placebo N=138
Age (years)			
Mean (SD)	14 (2)	15 (2)	14 (2)
Sex n (%)			
Female	44 (35)	45 (34)	50 (36)
Male	81 (65)	89 (66)	88 (64)
Race n (%)			
White	118 (94)	124 (93)	126 (91)
Black/African American	5 (4)	4 (3)	5 (4)
Asian	2 (2)	5 (4)	6 (4)
American Indian/Alaska Native	0	1 (1)	1 (1)
Height (cm)			
Mean (SD)	165 (10)	167 (11)	166 (11)
Weight (kg)			
Mean (SD)	60 (16)	61 (13)	57 (12)
Smoking History, N (%)			
Never smoked	125 (100)	134 (100)	137 (99)
Ex-smoker	0	0	1 (1)

Source: Reviewer Analysis

3.2.3.5 Study 456

The summary of the patient disposition in study 456 is given in Table 12. The majority of the patients completed this study with only 4 patients withdrawing from the study medication. The primary reason for discontinuation was noncompliant with protocol where there were 2 patients which were both in the placebo group.

Table 12 Disposition in Study 456

	Spiriva Respimat 2.5 mcg N (%)	Spiriva Respimat 5 mcg N (%)	Placebo N (%)
Randomized	127	130	135
TS	127 (100)	130 (100)	135 (100)
FAS	127 (100)	130 (100)	135 (100)
Completed	126 (99)	130 (100)	132 (98)
Discontinued	1 (1)	0	3 (2)
Adverse Event	0	0	1 (1)
Worsening of disease under study	0	0	0
Worsening of other pre-existing disease	0	0	0
Other AE	0	0	1 (1)
Lack of Efficacy	0	0	0
Non-compliant with protocol	0	0	2 (2)
Lost to Follow-Up	0	0	0
Consent withdrawn (not due to AE)	0	0	0
Other	1 (1)	0	0

Source: Reviewer Analysis

The demographics and baseline characteristics in study 456 are summarized for the TS population in Table 13. The patients' mean age was about 14 years. Most of the patients were White (95%). These factors were generally well-balanced across the treatment groups.

Table 13 Demographics in Study 456- Treated Set

	Spiriva Respimat 2.5 mcg N=127	Spiriva Respimat 5 mcg N=130	Placebo N=135
Age (years)			
Mean (SD)	14 (2)	14 (2)	14 (2)
Sex n (%)			
Female	47 (37)	47 (36)	56 (42)
Male	80 (63)	83 (64)	79 (59)
Race n (%)			
White	123 (97)	122 (94)	126 (93)
Black/African American	2 (2)	2 (2)	4 (3)
Asian	2 (2)	5 (4)	3 (2)
American Indian/Alaska Native	0	1 (1)	2 (2)
Hawaiian/Pacific Isle	0	0	0
Height (cm)			
Mean (SD)	164 (11)	165 (11)	162 (10)
Weight (kg)			
Mean (SD)	57 (16)	59 (17)	56 (16)
Smoking History, N (%)			
Never smoked	127 (100)	130 (100)	135 (100)

Source: Reviewer Analysis

3.2.4 Results and Conclusions

The applicant performed an interim analysis to reassess sample size based on time to first severe asthma exacerbation, the third primary endpoint in studies 416 and 417. The results from this analysis indicated the sample size should be increase to 200 patients per group in each study. Post-hoc, the applicant used the increased sample size to analyze the first two primary endpoints for the primary analysis without any adjustments to the overall type 1 to account for the interim analysis.

Since the applicant's interim analysis did not consider all primary endpoints, it was only based on exacerbations (section 3.3); I adjusted the primary analyses using a conservative method, the Bonferroni procedure for multiple comparisons. Since the overall significance level was 0.05, the adjusted significance level by Bonferroni method was 0.0167 which was used for the comparison of Spiriva Respimat with placebo.

3.2.4.1 Study 416

The results from the first two primary efficacy analyses are discussed in the order of the hierarchical testing procedure. Change from baseline in FEV_1 $peak_{0\text{-}3h}$ was tested first, if significant, change from baseline in trough FEV_1 was tested. See Table 14 for results.

Spiriva Respimat treatment demonstrated a statistically significant improvement in the mean change from baseline in FEV_1 $peak_{0\text{-}3h}$ compared to the placebo group, 0.40 L versus 0.32 L, respectively.

Since the comparison for the first primary endpoint, change from baseline in FEV_1 $peak_{0\text{-}3h}$ was statistically significant for Spiriva Respimat and according to the pre-specified multiplicity plan; inferential statistical analysis may proceed to the second primary endpoint, trough FEV_1. Spiriva Respimat demonstrated a statistically significant improvement in the mean change from baseline in trough FEV_1 compared to placebo, 0.14L versus 0.06L, respectively (see Table 14).

Based on the Bonferroni adjustment, Spiriva Respimat demonstrated a statistically significant improvement in the mean change from baseline for both of the first two primary endpoints.

There were very few patients with missing data. Most were due to going off treatment, 29 (6%) patients.

Table 14 Primary Efficacy Results (FAS)

	Spiriva Respimat N=217		Placebo N=211
FEV_1 $peak_{0\text{-}3h}$ (L) at 24 weeks			
Mean at week 24	0.40		0.32
Mean Treatment Δ from placebo		0.09	
95%CI		0.02, 0.15	
p-value		0.0110	
Trough FEV_1 (L) at 24 weeks			
Mean at week 24	0.14		0.06
Mean Treatment Δ from placebo		0.09	
95%CI		0.03, 0.15	
p-value		0.0050	

N: Number of observations used in the analysis
Source: Clinical Trial Report-Protocol Number 205.416 Table 11.4.1.1.1:1, page 116

Per clinical request the results for the secondary endpoints, time to first severe exacerbation and time to first symptomatic asthma exacerbation are included. There were no pre-specified multiplicity corrections in place for these secondary endpoints. The results are described for descriptive purposes only and the p-values reported are considered nominal. Time to first severe asthma exacerbation is shown in Table 15. There were fewer patients in the Spiriva Respimat group that had a severe asthma exacerbation compared to the placebo group. For the placebo group the time to first severe asthma exacerbation for the first quartile of patients was 233 days. The first quartile could not be calculated for the Spiriva Respimat groups due to less than 25% of the patients experiencing a severe asthma exacerbation.

Table 15 Time to First Severe Exacerbations (FAS)

	Spiriva Respimat N=237	Placebo N=222
n (%)	53 (22%)	68 (31%)
Hazard Ratio vs. placebo	0.70	
95% CI	0.49, 1.00	
p-value	0.0499	

Source: Clinical Trial Report-Protocol Number 205.416 Table 15.2.1.3:1, page 328

Time to first symptomatic asthma exacerbations are shown in Table 16. There were fewer patients in the Spiriva Respimat group that had a symptomatic asthma exacerbation compared to the placebo group. Time to first symptomatic asthma exacerbation for the first quartile of patients was 109 days for placebo and 175 days for Spiriva Respimat.

Table 16 Time to First Symptomatic Asthma Exacerbation (FAS)

	Spiriva Respimat N=237	Placebo N=222
n (%)	82 (35%)	99 (45%)
Hazard Ratio vs. placebo	0.75	
95% CI	0.56, 1.00	
p-value	0.0514	

Source: Clinical Trial Report-Protocol Number 205.416 Table 15.2.1.3:10, page 337

3.2.4.2 Study 417

The results from the first two primary efficacy analyses are demonstrated in the order of the hierarchical testing procedure. Change from baseline in FEV_1 $peak_{0\text{-}3h}$ was tested first, if significant, change from baseline in trough FEV_1 was tested. See Table 17 for results.

Spiriva Respimat demonstrated a statistically significant improvement in the mean change from baseline in FEV_1 $peak_{0\text{-}3h}$ compared to the placebo group, 0.40 L versus 0.25 L, respectively.

Since the comparison for the first primary endpoint, change from baseline in FEV_1 $peak_{0\text{-}3h}$ was statistically significant for the Spiriva Respimat group and according to the pre-specified multiplicity plan; inferential statistical analysis may proceed to the second primary endpoint, trough FEV_1. Spiriva Respimat demonstrated a statistically significant improvement in the mean change from baseline in trough FEV_1 compared to placebo, 0.16L versus 0.04L, respectively (see Table 17).

Based on Bonferroni's adjustment, Spiriva Respimat showed a statistically significant improvement in the mean change from baseline for both of the first two primary endpoints.

Table 17 Primary Efficacy Results (FAS)

	Spiriva Respimat N=216*	Placebo N=232*
FEV_1 $peak_{0-3h}$ (L) at 24 weeks		
N*	205	218
Mean at week 24	0.40	0.25
Mean Treatment Δ from placebo	0.15	
95%CI	0.09, 0.22	
p-value	<0.0001	
Trough FEV_1 (L) at 24 weeks		
N*	204	218
Mean at week 24	0.16	0.04
Mean Treatment Δ from placebo	0.11	
95%CI	0.05, 0.17	
p-value	0.0002	

N: Number of observations used in the analysis
Source: Clinical Trial Report-Protocol Number 205.417 Table 11.4.1.1.1:1, page 117

Per clinical request, the results for the secondary endpoints time to first severe exacerbation and time to first symptomatic asthma exacerbation are included. There were no pre-specified multiplicity corrections in place for any of the secondary endpoints. The results are included for descriptive purposes only and the p-values reported are considered nominal.

Time to first severe asthma exacerbation is shown in Table 18. There were fewer patients in the Spiriva Respimat group that had a severe asthma exacerbation compared to the placebo group. For the placebo group the time to first severe asthma exacerbation for the first quartile of patients was 224 days and 232 days for Spiriva Respimat.

Table 18 Time to First Severe Asthma Exacerbations (FAS)

	Spiriva Respimat N=216	Placebo N=232
n (%)	69 (32%)	81 (35%)
Hazard Ratio vs. placebo	0.89	
95% CI	0.65, 1.23	
p-value	0.4788	

Source: Clinical Trial Report-Protocol Number 205.417 Table 15.2.1.3:1, page 336

Time to first symptomatic asthma exacerbations are shown in Table 19. There were fewer patients in the Spiriva Respimat group that had a symptomatic asthma exacerbation compared to the placebo group. There was a significant difference between the groups in favor of Spiriva Respimat. Spiriva Respimat reduced the risk of symptomatic asthma exacerbation by 27% compared to placebo. Time to first symptomatic asthma exacerbation for the first quartile of patients was 111 days for placebo and 152 days for Spiriva Respimat. The median was 304 days

for placebo. The median could not be calculated for Spiriva Respimat since less than 50% of the patients had a symptomatic asthma exacerbation.

Table 19 Time to First Symptomatic Asthma Exacerbation

	Spiriva Respimat N=216	Placebo N=232
n (%)	86 (40%)	117 (50%)
Hazard Ratio vs. placebo	0.73	
95% CI	0.55, 0.96	
p-value	0.0234	

Source: Clinical Trial Report-Protocol Number 205.416 Table 15.2.1.3:10, page 337

3.2.4.3 Combined Studies 416 and 417

In order to obtain adequate number of events it was stated in both protocols that the analysis population for the third primary endpoint, time to first severe exacerbation, would use the combined results from studies 416 and 417. Additionally, the first two primary endpoints, change from baseline in FEV_1 $peak_{0\text{-}3h}$ after 24 weeks and change from baseline in trough FEV_1 after 24 weeks, were required to be significant in both studies. Since the first two primary endpoints were significant in both studies, inferential statistical analysis proceeded to the third primary endpoint, time to first severe asthma exacerbation.

Table 20 shows the results for time to first severe asthma exacerbation. Before the adjustment for the interim analysis, there was no statistically significant difference between Spiriva Respimat and placebo. There was a numerical treatment benefit for Spiriva Respimat over placebo. This concurs with the results from studies 416 and 417. However, after the adjustment for the pre-planned unblinded interim analysis, there was a statistically significant difference in favor of Spiriva Respimat. Spiriva Respimat reduced the risk of severe asthma exacerbations by 21% compared to placebo.

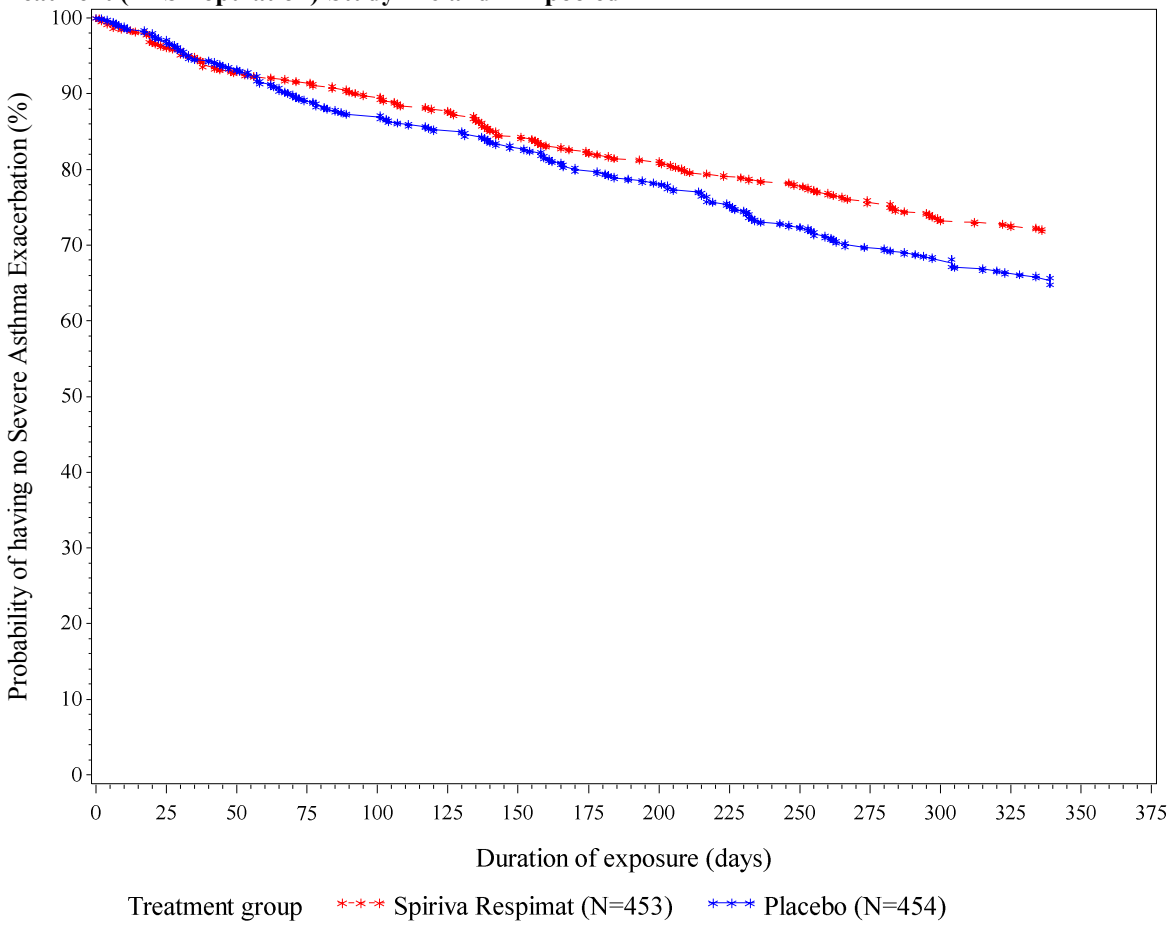
Table 20 Time to First Severe Asthma Exacerbation (FAS)

	Spiriva Respimat N=453	Placebo N=454
n (%)	122 (27%)	149 (33%)
Hazard Ratio vs. placebo	0.79	
95% CI	0.62, 1.00	
p-value	0.0535	
adjusted p-value	0.0343	

n: Number of exacerbations observed
Source: Clinical Trial Report-Protocol Number 205.416 and 205.417 Table 15.2.1.1.1:1, page 101

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

Figure 1 Kaplan-Meier Estimates of the Probability of No Severe Asthma Exacerbation during Randomized Treatment (FAS Population)-Study 416 and 417 pooled



Source: Reviewer Analysis

Per clinical request the results for the secondary endpoint, time to first symptomatic asthma exacerbation is included, see Table 21. There were no pre-specified multiplicity corrections in place for any of the secondary endpoints. The results are described for descriptive purposes only and the p-values reported are nominal p-values.

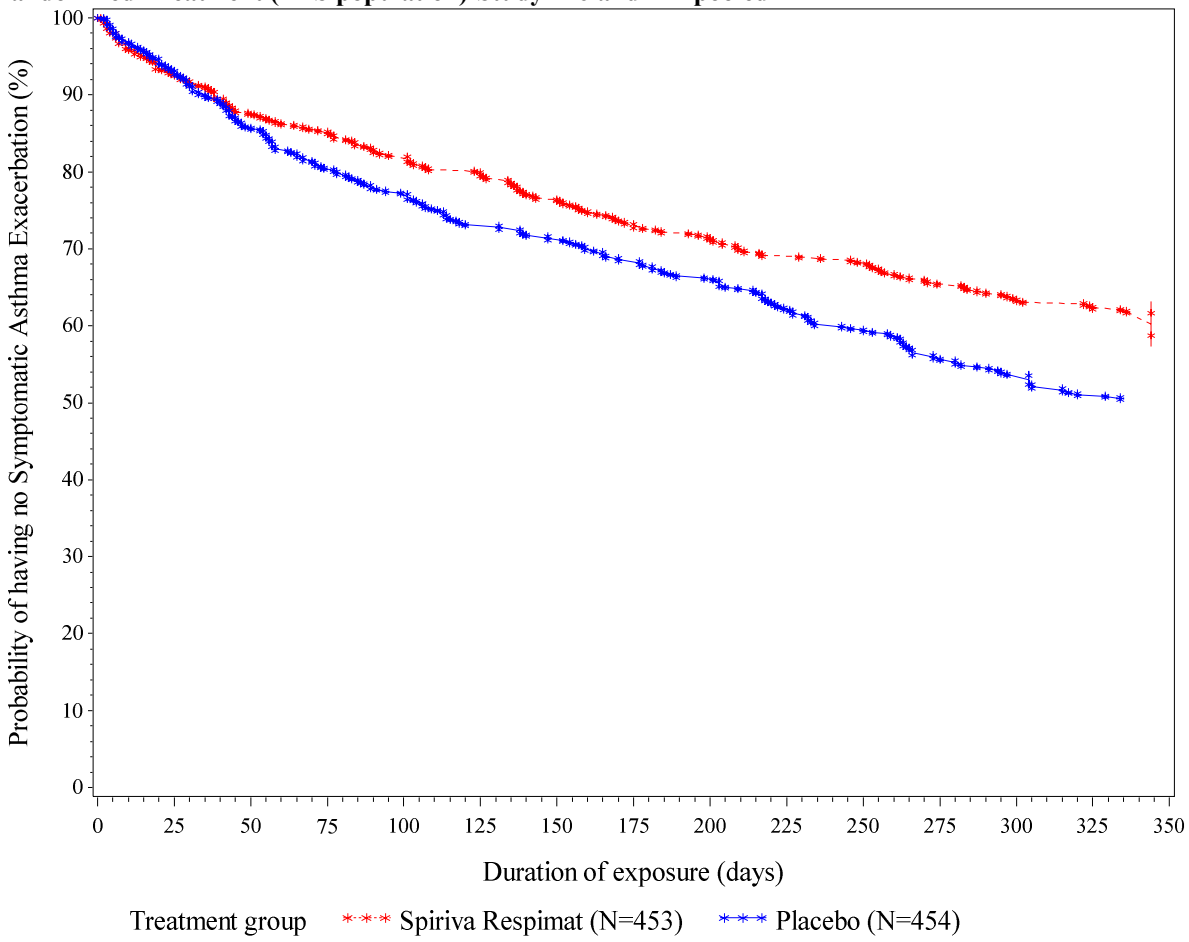
Table 21 Time to First Symptomatic Asthma Exacerbation (FAS)

	Spiriva Respimat N=453	Placebo N=454
n (%)	168 (37%)	216 (48%)
Hazard Ratio vs. placebo	0.73	
95% CI	0.60, 0.90	
p-value	0.0024	

n: Number of exacerbations observed
Source: Clinical Trial Report-Protocol Number 205.416 and 205.417 Table 15.2.1.1.2:9, page 116

The Kaplan-Meier plot of time to first symptomatic asthma exacerbation is shown in Figure 2.

Figure 2 Kaplan-Meier Estimated of the Probability of No Symptomatic Asthma Exacerbation during Randomized Treatment (FAS population)-Study 416 and 417 pooled



Source: Reviewer Analysis

3.2.4.4 Study 418

The results from the first two primary efficacy analyses are shown in Table 22. Spiriva Respimat 5 mcg showed a statistically significant improvement in the mean change from baseline in FEV_1 $peak_{0\text{-}3h}$ compared to placebo, 0.25L versus 0.05L, respectively. There was also a significant improvement of Spiriva Respimat over placebo for trough FEV_1, 0.12L versus -0.04L, respectively. There was also a statistically significant improvement for both change from baseline in FEV_1 $peak_{0\text{-}3h}$ and trough FEV_1 for Spiriva Respimat 2.5 mcg over placebo. For both the primary endpoints Spiriva Respimat 2.5 mcg demonstrated a slightly greater mean treatment effect over placebo than Spiriva Respimat 5 mcg.

Table 22 Primary Efficacy Results (FAS)

	SR 5 N=241	SR 2.5 N=247	Salmeterol N=259	Placebo N=250
FEV_1 $peak_{0\text{-}3h}$ (L) at 24 weeks				
Mean at week 24	0.25	0.29	0.27	0.05
Mean Treatment Δ from placebo	0.20	0.24	0.21	
95% CI	0.14, 0.25	0.18, 0.29	0.16, 0.27	
p-value	<0.0001	<0.0001	<0.0001	
Trough FEV_1 (L) at 24 weeks				
Mean at week 24	0.12	0.15	0.09	-0.04
Mean Treatment Δ from placebo	0.15	0.19	0.12	
95% CI	0.09, 0.21	0.13, 0.24	0.06, 0.18	
p-value	<0.0001	<0.0001	<0.0001	

N: Number of observations used in the analysis
Source: Clinical Trial Report-Protocol Number 205.418 Table 11.4.1.1.1:1, page 122

Per clinical request, the results for the secondary endpoint time to first severe asthma exacerbation are included. There were no pre-specified multiplicity corrections in place for any of the secondary endpoints. The results are described for descriptive purposes only and the p-values reported are considered nominal.

Time to first severe asthma exacerbation is shown in Table 23. There were fewer patients in both Spiriva Respimat groups that had a severe asthma exacerbation compared to the placebo group. There were fewer severe asthma exacerbations on Spiriva Respimat 2.5 mcg than Spiriva Respimat 5 mcg. The median time to first severe asthma exacerbation could not be calculated for any of the treatment groups since less than 50% of the patients had a severe asthma exacerbation.

Table 23 Secondary Efficacy Results Time to First Severe Asthma Exacerbation- 24 weeks (FAS)

	SR 5 N=261	SR 2.5 N=259	Salmeterol N=271	Placebo N=265
n (%)	17 (7)	9 (3)	14 (5)	24 (9)
Active vs Placebo Hazard Ratio	0.72	0.37	0.55	
95% CI	0.39, 1.35	0.17, 0.80	0.29, 1.07	
p-value	0.3062	0.0112	0.0798	

Source: 16.1.9 Documentation of Statistical-Bioanalytical and Pharmacokinetic Analysis Protocol Number- 205.418 Table 6.1.4.15, page 1866

3.2.4.5 Study 419

Results from the analyses of the first two primary efficacy endpoints are shown in Table 24. Both doses of Spiriva Respimat demonstrated a statistically significant improvement in the mean change from baseline in FEV_1 $peak_{0-3h}$ and trough FEV_1 when compared to placebo. Additionally, for both primary endpoints Spiriva Respimat 2.5 mcg demonstrated a slightly greater mean treatment effect over placebo than Spiriva Respimat 5 mcg.

Table 24 Primary Efficacy Results (FAS)

	SR 5 N=240	SR 2.5 N=245	Salmeterol N=251	Placebo N=242
FEV_1 $peak_{0-3h}$ (L) at 24 weeks				
Mean at week 24	0.24	0.29	0.25	0.08
Mean Treatment Δ from placebo	0.17	0.21	0.18	
95% CI	0.12, 0.22	0.16, 0.26	0.12, 0.23	
p-value	<0.0001	<0.0001	<0.0001	
Trough FEV_1 (L) at 24 weeks				
Mean at week 24	0.12	0.16	0.09	-0.01
Mean Treatment Δ from placebo	0.13	0.18	0.11	
95% CI	0.08, 0.19	0.12, 0.23	0.05, 0.16	
p-value	<0.0001	<0.0001	0.0002	

N: Number of observations used in the analysis
Source: Clinical Trial Report-Protocol Number 205.419 Table 11.4.1.1.1:1, page 123

Per clinical request, the results for the secondary endpoint time to first severe asthma exacerbation are included. There were no pre-specified multiplicity corrections in place for any of the secondary endpoints. The results are described for descriptive purposes only and p-values are considered nominal.

Time to first severe asthma exacerbation is shown in Table 25. There were fewer patients in both Spiriva Respimat groups that had a severe asthma exacerbation compared to the placebo group and there were fewer severe asthma exacerbations for patients on Spiriva Respimat 2.5 mcg than Spiriva Respimat 5 mcg. The median time to first severe asthma exacerbation could not be calculated for any of the treatment groups since less than 50% of the patients had a severe asthma exacerbation.

Table 25 Secondary Efficacy Results Time to First Severe Asthma Exacerbation- 24 weeks (FAS)

	SR 5 N=252	SR 2.5 N=256	Salmeterol N=264	Placebo N=253
n (%)	14 (6)	13 (5)	20 (8)	19 (8)
Active vs Placebo				
Hazard Ratio	0.72	0.66	1.00	
95% CI	0.36, 1.43	0.33, 1.35	0.53, 1.87	
p-value	0.3492	0.2555	0.9990	

Source: 16.1.9.2 Documentation of Statistical-Bioanalytical and Pharmacokinetic Analysis Protocol Number-205.419 Table 6.1.4.15, page 1903

3.2.4.6 Combined Studies 418 and 419

The pre-specified primary efficacy analysis for the first two primary endpoints in studies 418 and 419, change from baseline in FEV_1 $peak_{0-3h}$ and trough FEV_1, demonstrated a significant treatment effect for Spiriva Respimat 5 mcg. Therefore, according to the pre-specified multiplicity plan, inferential statistical analysis may proceed to the third primary endpoint, ACQ response. Table 26 shows the results for ACQ response after 24 weeks. Spiriva Respimat showed a statistically significant improvement over placebo.

Table 26 Primary Efficacy Results ACQ Responder after 24 Weeks (FAS)

	SR 5 N=513	SR 2.5 N=515	Salmeterol N=535	Placebo N=518
Number of responders (%)	330 (64)	332 (65)	356 (67)	299 (58)
Active vs Placebo				
Odds Ratio	1.32	1.33	1.46	
95% CI	1.02, 1.71	1.03, 1.72	1.13, 1.89	
p-value	0.0348	0.0308	0.0039	

N: Number of patients with measurements available at week 24 in the full analysis set.
Source: Clinical Trial Report-Protocol Number 205.418 and 205.419 Table 11.4.1.1.1:1, page 54

Per clinical request the results for the secondary endpoint time to first severe asthma exacerbation are included. There were no pre-specified multiplicity corrections in place for any of the secondary endpoints. The results are described for descriptive purposes only and p-values are considered nominal.

Time to first severe asthma exacerbation is shown in Table 27. There were fewer patients in both Spiriva Respimat groups that had a severe asthma exacerbation compared to the placebo group and there were fewer severe asthma exacerbations for patients on Spiriva Respimat 2.5 mcg than in Spiriva Respimat 5 mcg. The median time to first severe asthma exacerbation could not be calculated for any treatment group since less than 50% of the patients had a severe asthma exacerbation.

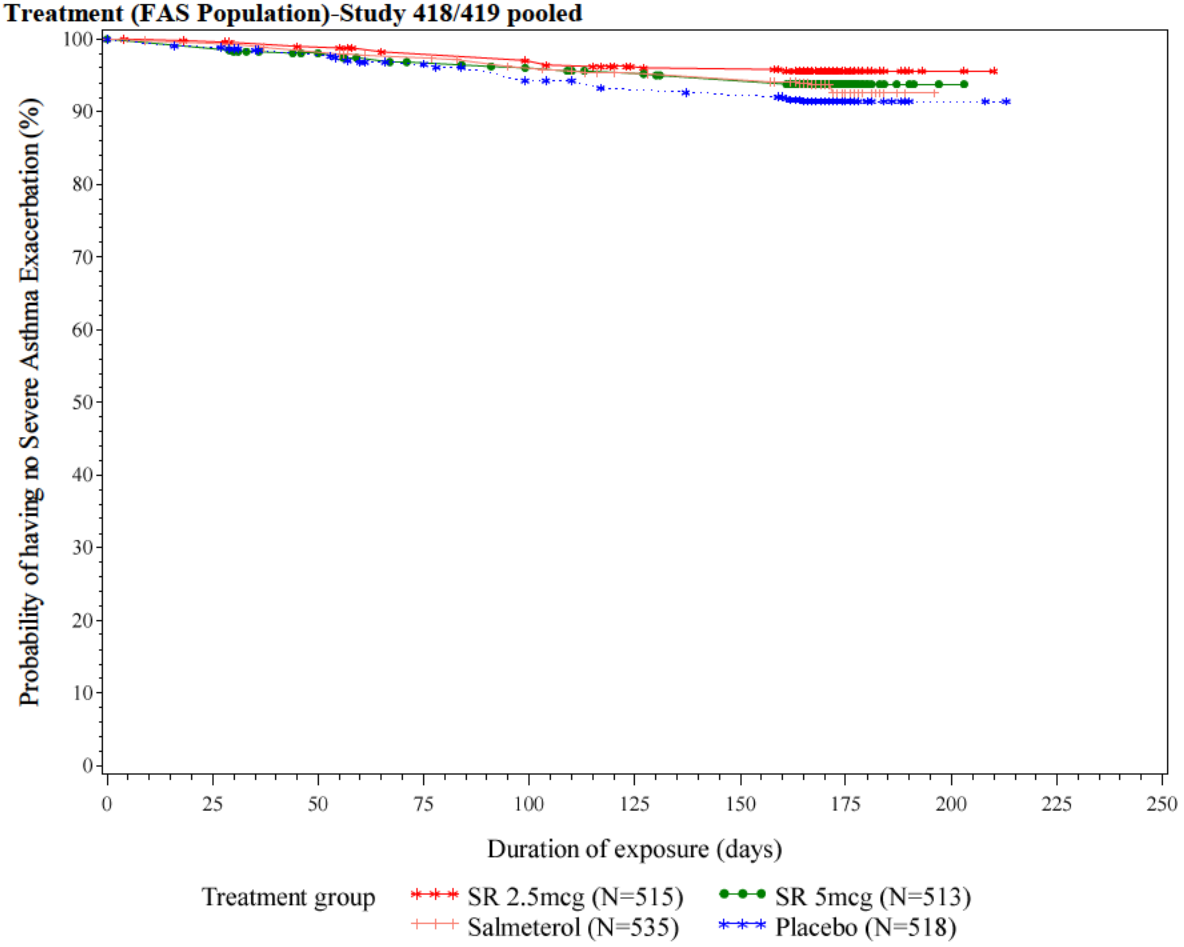
Table 27 Secondary Efficacy Results Time to First Severe Asthma Exacerbation- 24 weeks (FAS)

	SR 5 N=513	SR 2.5 N=515	Salmeterol N=535	Placebo N=518
n (%)	31 (6)	22 (4)	34 (6)	43 (8)
Active vs Placebo				
Hazard Ratio	0.72	0.50	0.75	
95% CI	0.45, 0.72	0.30, 0.84	0.48, 1.18	
p-value	0.1644	0.0084	0.2149	

Source: 16.1.9 Documentation of Statistical-Bioanalytical and Pharmacokinetic Analysis Protocol Number- 205.418 and 205.419 Table 6.2.1, page 221

The Kaplan-Meier plot of time to first severe asthma exacerbation is shown in Figure 3.

Figure 3 Kaplan-Meier Estimates of the Probability of No Severe Asthma Exacerbation during Randomized Treatment (FAS Population)-Study 418/419 pooled



Source: Reviewer Analysis

3.2.4.7 Study 442

The results from the primary efficacy analysis are shown in Table 28. Spiriva Respimat 5 mcg demonstrated a statistically significant improvement in the mean change from baseline in FEV_1 $peak_{0-3h}$ compared to placebo, 0.26L versus 0.13L, respectively. Since the comparison for the highest dose of Spiriva Respimat for the primary endpoint was statistically significant and according to the pre-specified multiplicity plan; inferential statistical analysis proceeded to testing the primary endpoint at the lower dose. Spiriva Respimat 2.5 mcg also demonstrated a statistically significant improvement in the mean change from baseline in FEV_1 $peak_{0-3h}$ compared to placebo, 0.29L versus 0.13L, respectively. Numerically, Spiriva Respimat 2.5 mcg demonstrated a slightly greater mean treatment effect over placebo than Spiriva Respimat 5 mcg.

The results for the key secondary endpoint, trough FEV_1 is included to support the bronchodilator indication. There were no pre-specified multiplicity corrections in place for this endpoint. There was a significant improvement of Spiriva Respimat in both the 5 mcg and the 2.5 mcg doses over placebo for trough FEV_1.

Table 28 Primary and Key Secondary Efficacy Results (FAS)

	SR 5 N=152	SR 2.5 N=151	Placebo N=154
FEV_1 $peak_{0-3h}$ (L) at 12 weeks			
Mean at week 12	0.26	0.29	0.13
Mean Treatment Δ from placebo	0.13	0.16	
95% CI	0.06, 0.20	0.09, 0.23	
p-value	0.0005	<0.0001	
Trough FEV_1 (L) at 12 weeks			
Mean at week 12	0.14	0.13	0.02
Mean Treatment Δ from placebo	0.12	0.11	
95% CI	0.05, 0.19	0.04, 0.18	
p-value	0.0010	0.0028	

N: Number of observations used in the analysis
Source: Clinical Trial Report-Protocol Number 205.442 Table 11.4.1.1.1:1, page 92 and Table 11.4.1.2.1:1, page 94

3.2.4.8 Study 444

The results from the primary efficacy analysis are shown in Table 29. Spiriva Respimat 5 mcg demonstrated a statistically significant improvement in the mean change from baseline in FEV_1 $peak_{0-3h}$ compared to placebo, 0.55L versus 0.37L, respectively. Since the comparison for the highest dose of Spiriva Respimat for the primary endpoint was statistically significant and according to the pre-specified multiplicity plan; inferential statistical analysis proceeded to testing the primary endpoint for the lower dose. Spiriva Respimat 2.5 mcg also demonstrated a

statistically significant improvement in the mean change from baseline in FEV_1 $peak_{0\text{-}3h}$ compared to placebo, 0.51L versus 0.37L, respectively.

The results for the secondary endpoint, trough FEV_1 are included to support the bronchodilator indication. There were no pre-specified multiplicity corrections in place for this endpoint. The results are shown in Table 29. There was a greater numerical difference for Spiriva Respimat 5 mcg over placebo.

Table 29 Primary and Secondary Efficacy Results (FAS)

	SR 5 N=134	SR 2.5 N=125	Placebo N=138
FEV_1 $peak_{0\text{-}3h}$ (L) at 24weeks			
n*	131	130	137
Mean at week 12	0.55	0.51	0.37
Mean Treatment Δ from placebo	0.17	0.13	
95% CI	0.08, 0.27	0.03, 0.23	
p-value	0.0005	0.0085	
Trough FEV_1 (L) at 24 weeks			
n*	131	119	137
Mean at week 12	0.40	0.37	0.29
Mean Treatment Δ from placebo	0.12	0.08	
95% CI	0.01, 0.22	-0.03, 0.19	
p-value	0.0320	0.1307	

*n: Number of observations used in the analysis
Source: Clinical Trial Report-Protocol Number 205.444 Table 11.4.1.1.1:1, page 96 and Table 11.4.1.2.1:1, page 98

Per clinical request the results for the secondary endpoint time to first severe asthma exacerbation are included. There were no pre-specified multiplicity corrections in place for any of the secondary endpoints. The results are described for descriptive purposes only and the p-values reported are nominal p-values.

Time to first severe asthma exacerbation is shown in Table 30. There were fewer patients in both Spiriva Respimat groups that had a severe asthma exacerbation compared to the placebo group. The median time to first severe asthma exacerbation could not be calculated for any of the treatment groups since less than 50% of the patients had a severe asthma exacerbation.

Table 30 Secondary Efficacy Results Time to First Severe Asthma Exacerbation - 48 weeks (FAS)

	SR 5 N=134	SR 2.5 N=125	Placebo N=138
n (%)	2 (1)	5 (4)	9 (7)
Active vs Placebo			
Hazard Ratio	0.23	0.63	
95% CI	0.05, 1.1	0.21, 1.9	
p-value	0.0620	0.4023	

Source: 16.1.9.2 Documentation of Statistical-Bioanalytical and Pharmacokinetic Analysis Protocol Number-205.444 Table 6.2.3.2, page 1032

3.2.4.9 Study 456

The results from the primary efficacy analysis are shown in Table 31. Since both doses of Spiriva Respimat failed to demonstrate a statistically significant improvement in the mean change from baseline in FEV_1 $peak_{0\text{-}3h}$ compared to placebo, p-value > 0.025, no further comparison were considered Regardless of the hierarchical testing strategy, there was not a significant difference between either dose of Spiriva Respimat and placebo for trough FEV_1.

Table 31 Primary and Secondary Efficacy Results (FAS)

	SR 5 N=130	SR 2.5 N=127	Placebo N=135
FEV_1 $peak_{0\text{-}3h}$ (L) at 12 weeks			
n*	130	126	132
Mean at week 12	0.53	0.55	0.44
Mean Treatment Δ from placebo	0.09	0.11	
95% CI	-0.02, 0.20	0.002, 0.22	
p-value	0.1039	0.0457	
Trough FEV_1 (L) at 12 weeks			
n*	130	126	132
Mean at week 12	0.28	0.35	0.23
Mean Treatment Δ from placebo	0.05	0.12	
95% CI	-0.06, 0.17	-0.00, 0.23	
p-value	0.3605	0.0509	

*n: Number of observations used in the analysis
Source: Clinical Trial Report-Protocol Number 205.456 Table 11.4.1.1.1:1, page 104 and Table 11.4.1.2.1:1, page 107

3.3 Evaluation of Safety

Safety evaluations for this submission will be evaluated by the Medical Reviewer, Stacy Chin, M.D. Refer to her review for more details regarding the safety findings of Spiriva Respimat.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analysis on the primary and key secondary efficacy endpoints were performed by gender, age, race (Black or African American, American Indian or Alaskan Native, Asian, Hawaiian or Pacific Islander, and White) and region (US and Canada, other) in all of the studies. The subgroup analyses were performed using the FAS population.

Figures 4-21 in the appendix summarize the efficacy results by subgroups for studies 416, 417, 418, 419, 442, 444, and 456. In general, the subgroup analyses were consistent with the primary and key secondary results from the overall population. However, these studies were not designed or powered to detect differences in these specific groups.

There was some interest in the Black or African American subgroup. There were few patients in this subgroup in each study. Majority of the Black or African Americans were in the US and Canada. In general the treatment effect was consistent with the primary and key secondary results, except in studies 417 both primary endpoints (Figures 6 and 7, see Appendix), 419 for trough FEV_1 (Figure 15, see Appendix), and 444 for FEV_1 $peak_{0\text{-}3h}$ (Figure 19, see Appendix) each for Spiriva Respimat 5 mcg.

Note that study 442 was not conducted in the USA.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

During the course of this review, an information request (IR) was sent to the applicant. The IR requested information about the interim analysis in studies 416 and 417. The applicant submitted the dataset containing all the interim data for exacerbations along with a detailed description of the interim analysis including the Independent Data Monitoring Committee meeting minutes. I was able to replicate the results from the interim analysis.

In studies 416 and 417 the applicant performed an interim analysis to reassess sample size based on the third primary endpoint, time to first severe asthma exacerbation. The results from this analysis indicated the sample size should be increase to 200 patients per group in each study. Post-hoc, the applicant used the increased sample size to analyze the first two primary endpoints for the primary analysis without any adjustments to the overall type 1 error to account for the interim analysis. I adjusted the primary analysis using a conservative method, the Bonferroni procedure for multiple comparisons. Based on this adjustment, Spiriva Respimat demonstrated a statistically significant improvement in the mean change from baseline for both of the first two primary endpoints in both studies, which was consistent with the primary analysis. Note this was not a statistical issue.

The applicant did not pre-specify a comparison of Spiriva Respimat 2.5 mcg to 5 mcg. However, Spiriva Respimat 2.5 mcg numerically was better than the 5 mcg dose in most of the studies. Note Spiriva Respimat 2.5 mcg was not a treatment arm in studies 416 and 417.

5.2 Conclusions and Recommendations

In studies 416 and 417, the first two primary endpoints FEV_1 $peak_{0\text{-}3h}$ and trough FEV_1 at 24 weeks demonstrated a statistically significant treatment effect in favor of Spiriva Respimat 5mcg over placebo. The third primary endpoint, time to first severe asthma exacerbation after 48 weeks, was analyzed using the pooled data from studies 416 and 417, and demonstrated a statistically significant improvement for Spiriva Respimat over placebo once adjusted for the interim analysis. There was a 21% reduction in the risk of having a severe asthma exacerbation in a year for patients in the Spiriva Respimat 5mcg group compared to placebo group. However, as the pooled analysis is considered as evidence from one study, there was not replicated evidence of an exacerbation benefit for Spiriva Respimat 5 mcg.

In studies 418 and 419 the first two primary endpoints FEV_1 $peak_{0\text{-}3h}$ and trough FEV_1 at 24 weeks demonstrated a statistically significant treatment effect in favor of Spiriva Respimat regardless of dose. The third primary endpoint ACQ responder after 24 weeks demonstrated a statistically significant improvement over placebo in both Spiriva Respimat doses using the pooled data from studies 418 and 419. The secondary endpoint, time to first severe asthma exacerbation, in the pooled studies 418 and 419 did not demonstrate statistically significant improvements for Spiriva Respimat 5 mcg compared to placebo but did demonstrate significance for Spiriva Respimat 2.5 mcg compared to placebo.

In study 442 the primary endpoint, FEV_1 $peak_{0\text{-}3h}$, demonstrated a statistically significant treatment effect in both the high and low dose of Spiriva Respimat over placebo. The secondary endpoint, trough FEV_1, also demonstrated a statistically significant improvement in both doses for Spiriva Respimat over placebo. Note there were no pre-specified multiplicity corrections in place for any of the secondary endpoints.

The two adolescent studies, 444 and 456 did not replicate each other's results. In study 444, the primary endpoint, FEV_1 $peak_{0\text{-}3h}$, demonstrated a statistically significant treatment effect in both the high and low dose of Spiriva Respimat over placebo. For the secondary endpoint, trough FEV_1, Spiriva Respimat 5 mcg demonstrated a statistically significant improvement over placebo; however, the 2.5 mcg dose did not demonstrate a statistically significant improvement over placebo. The trend for the 2.5 mcg dose was in the right direction. The secondary endpoint, time to first severe asthma exacerbation, did not demonstrate a statistically significant improvement for either Spiriva Respimat dose over placebo. Note there were no pre-specified multiplicity corrections in place for any of the secondary endpoints in study 444. Where as in study 456, the primary endpoint FEV_1 $peak_{0\text{-}3h}$, did not demonstrated a statistically significant treatment effect in either the high or the low dose of Spiriva Respimat over placebo. Numerically, there was a slightly greater improvement in the Spiriva Respimat 2.5 mcg compared to placebo than seen in the Spiriva Respimat 5 mcg group.

Based on the results from these studies, the efficacy of Spiriva Respimat 2.5 mcg (b) (4) for the long-term, once daily, add-on maintenance treatment of asthma was demonstrated.

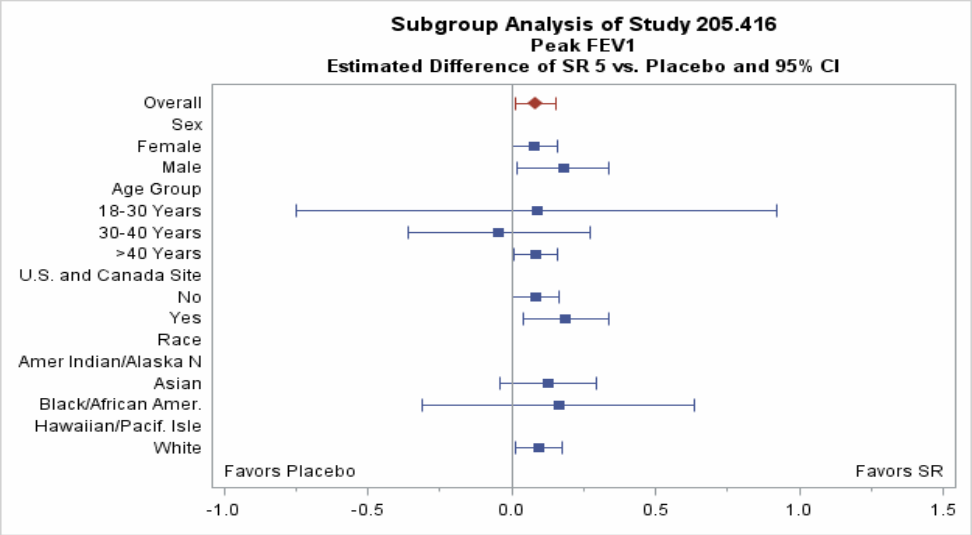
5.3 Comment on the Proposed Label

The following are suggestions for the applicant's proposed label.

(b) (4)

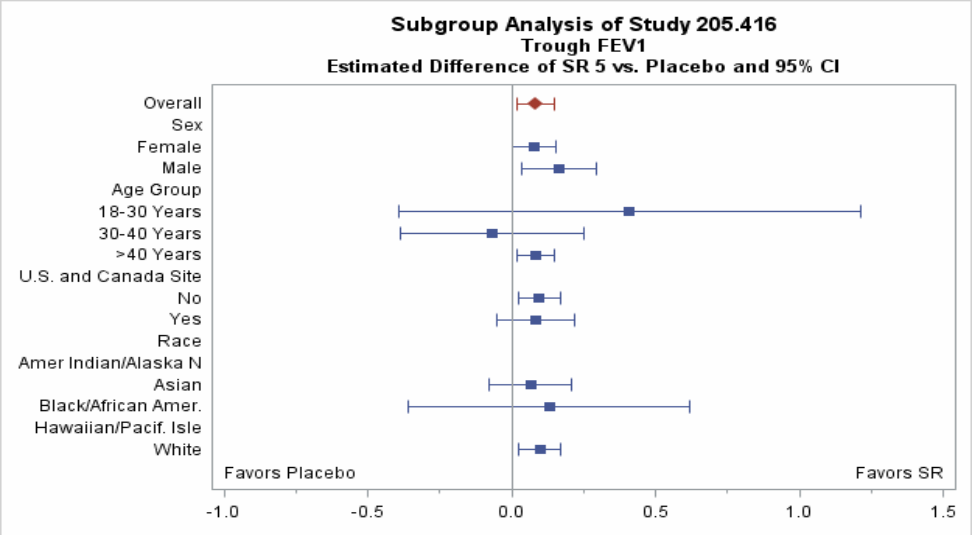
6 APPENDIX

Figure 4 Subgroup Analysis of Peak FEV_1- Study 416



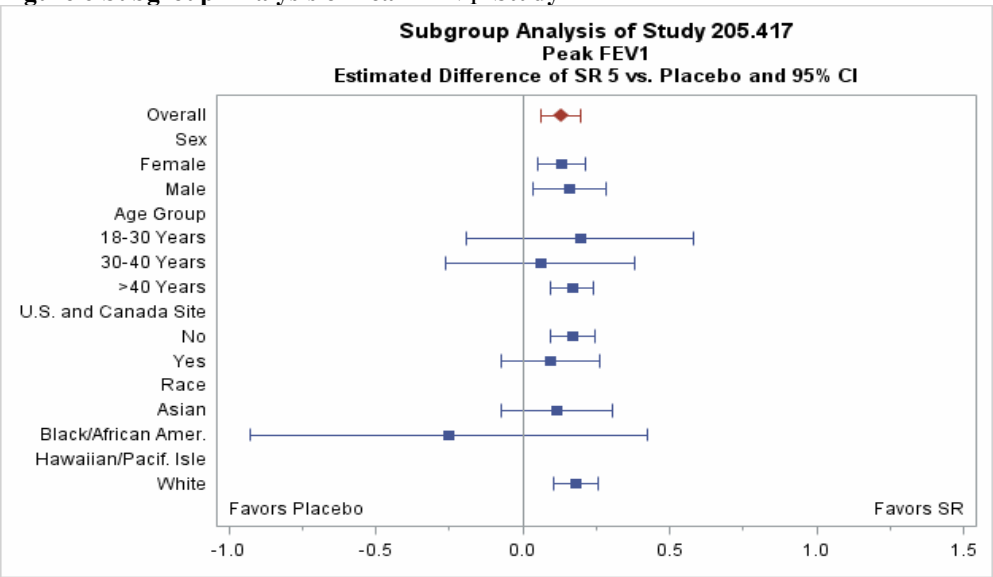
Source: Reviewer Analysis

Figure 5 Subgroup Analysis of Trough FEV_1- Study 416



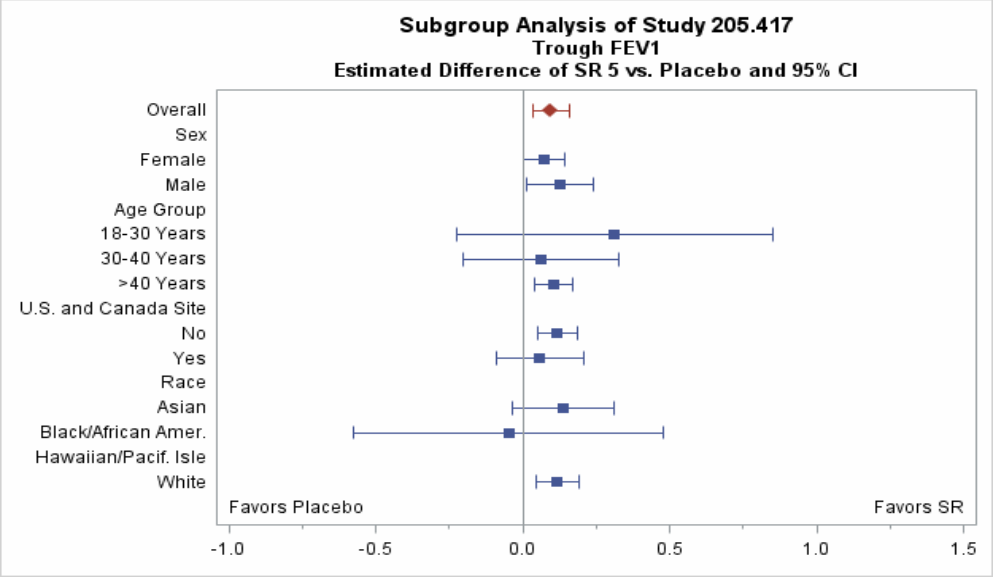
Source: Reviewer Analysis

Figure 6 Subgroup Analysis of Peak FEV_1- Study 417



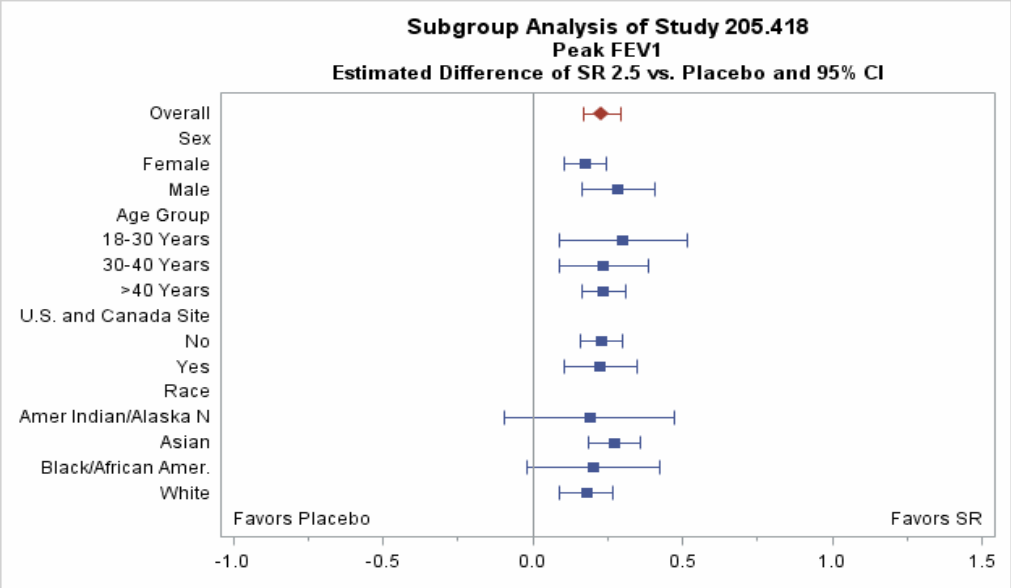
Source: Reviewer Analysis

Figure 7 Subgroup Analysis of Trough FEV_1- Study 417



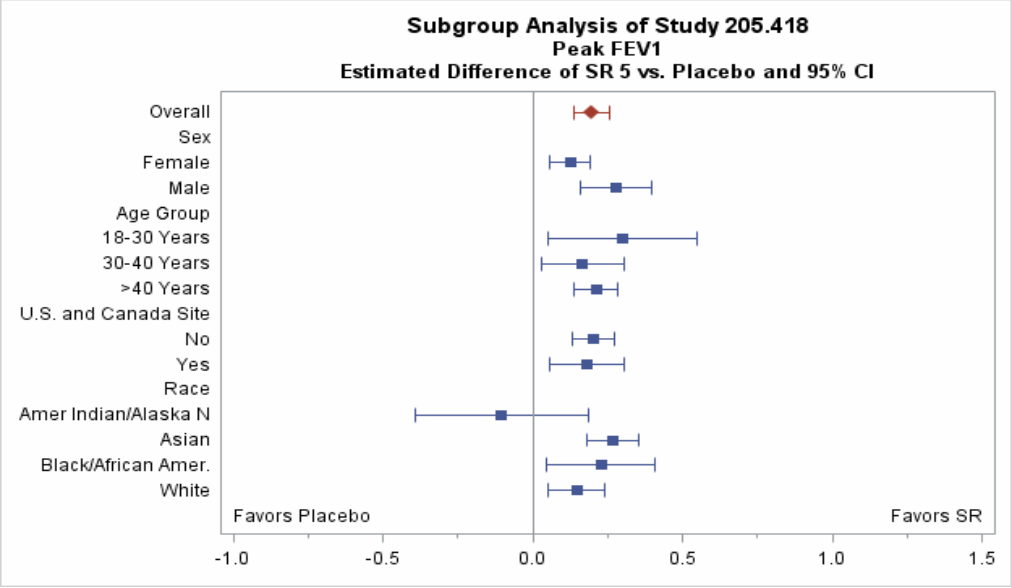
Source: Reviewer Analysis

Figure 8 Subgroup Analysis of Peak FEV_1 (Spiriva Respimat 2.5 mcg)- Study 418



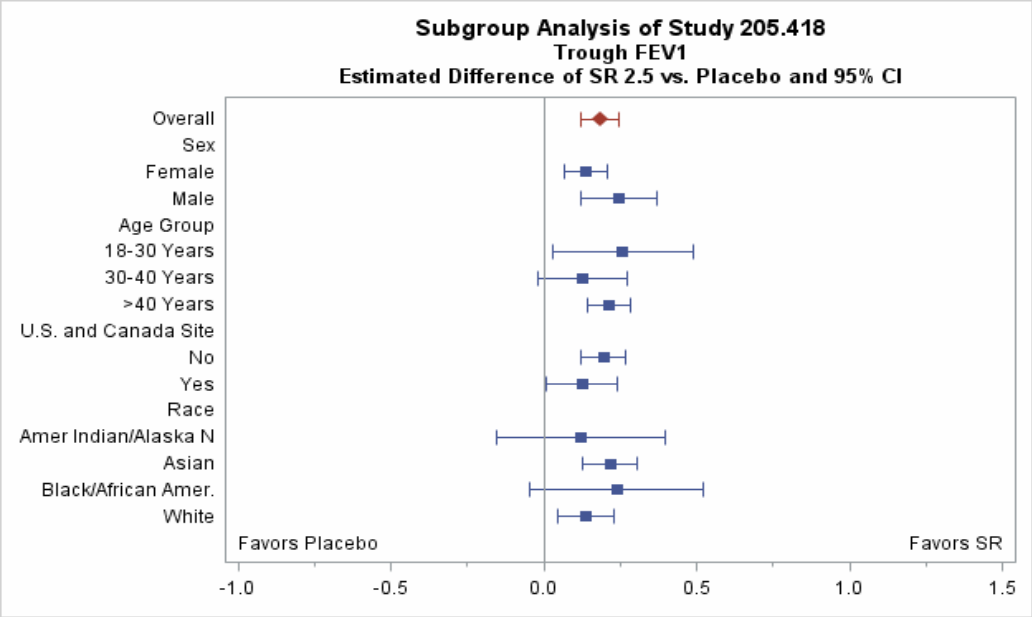
Source: Reviewer Analysis

Figure 9 Subgroup Analysis of Peak FEV_1 (Spiriva Respimat 5 mcg)- Study 418



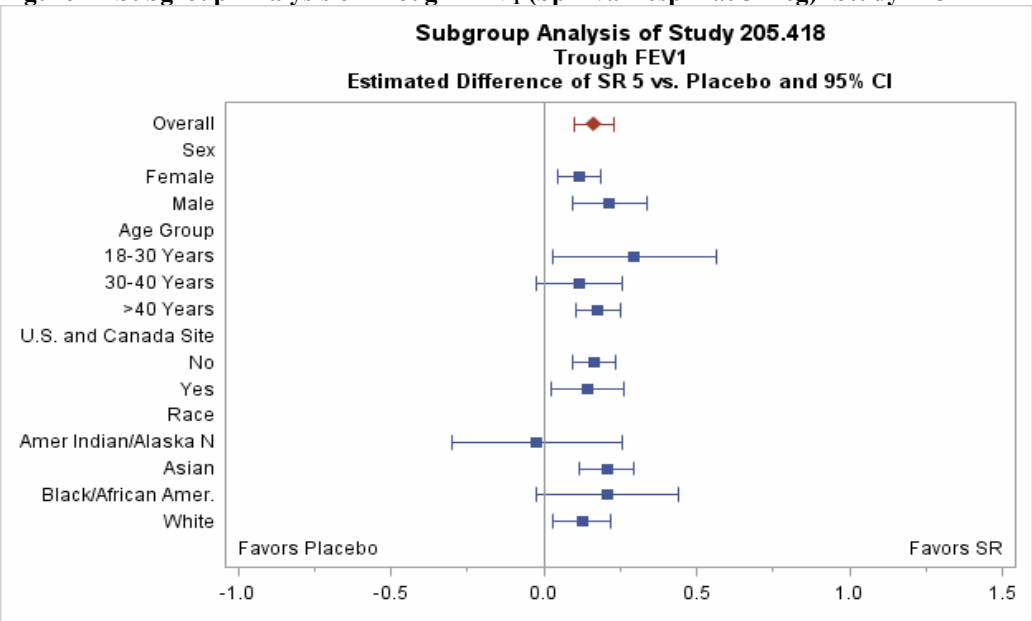
Source: Reviewer Analysis

Figure 10 Subgroup Analysis of Trough FEV_1 (Spiriva Respimat 2.5 mcg)- Study 418



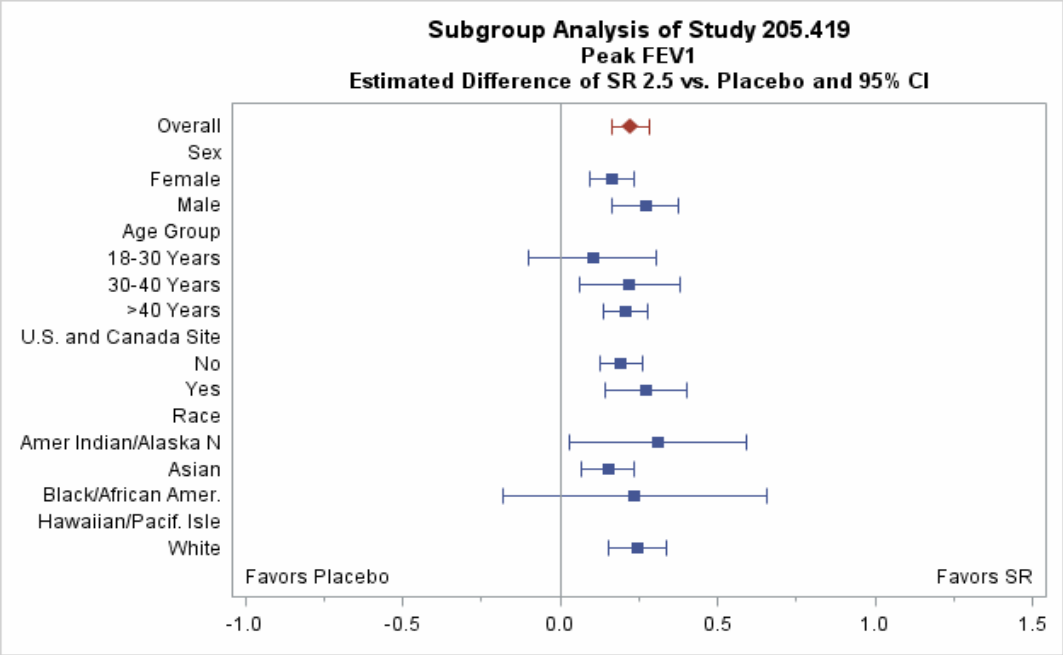
Source: Reviewer Analysis

Figure 11 Subgroup Analysis of Trough FEV_1 (Spiriva Respimat 5 mcg)- Study 418



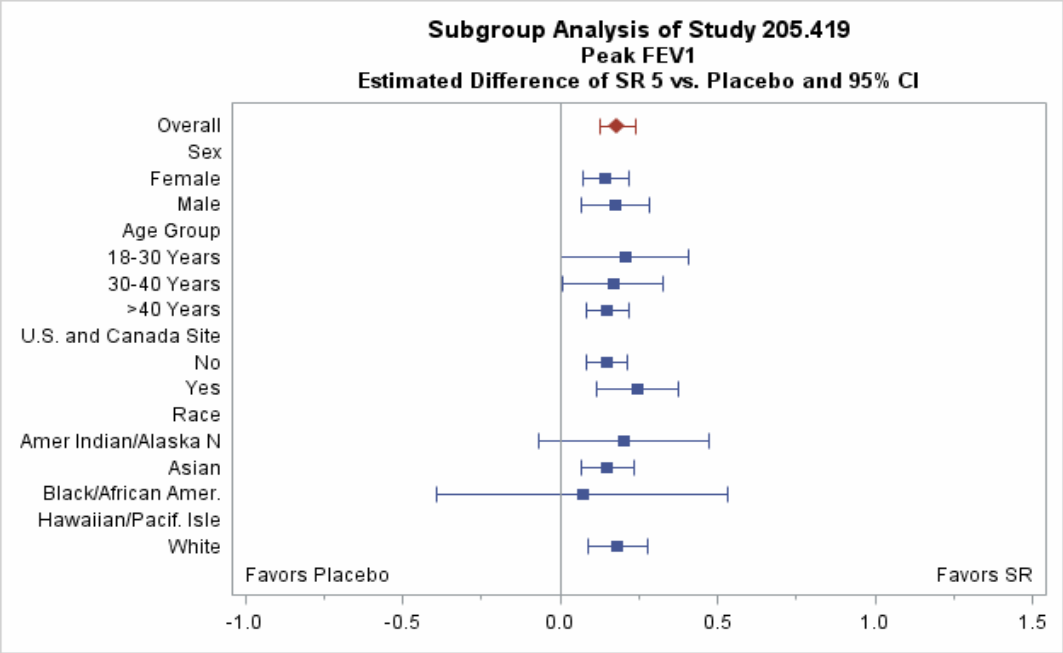
Source: Reviewer Analysis

Figure 12 Subgroup Analysis of Peak FEV_1 (Spiriva Respimat 2.5 mcg)- Study 419



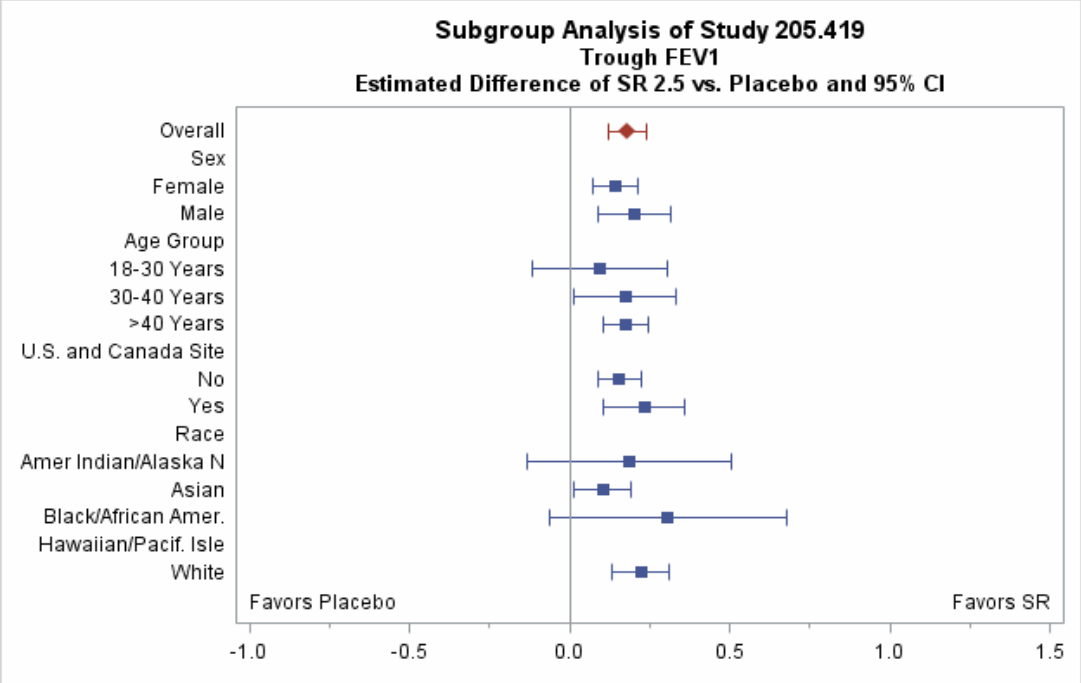
Source: Reviewer Analysis

Figure 13 Subgroup Analysis of Peak FEV_1 (Spiriva Respimat 5 mcg)- Study 419



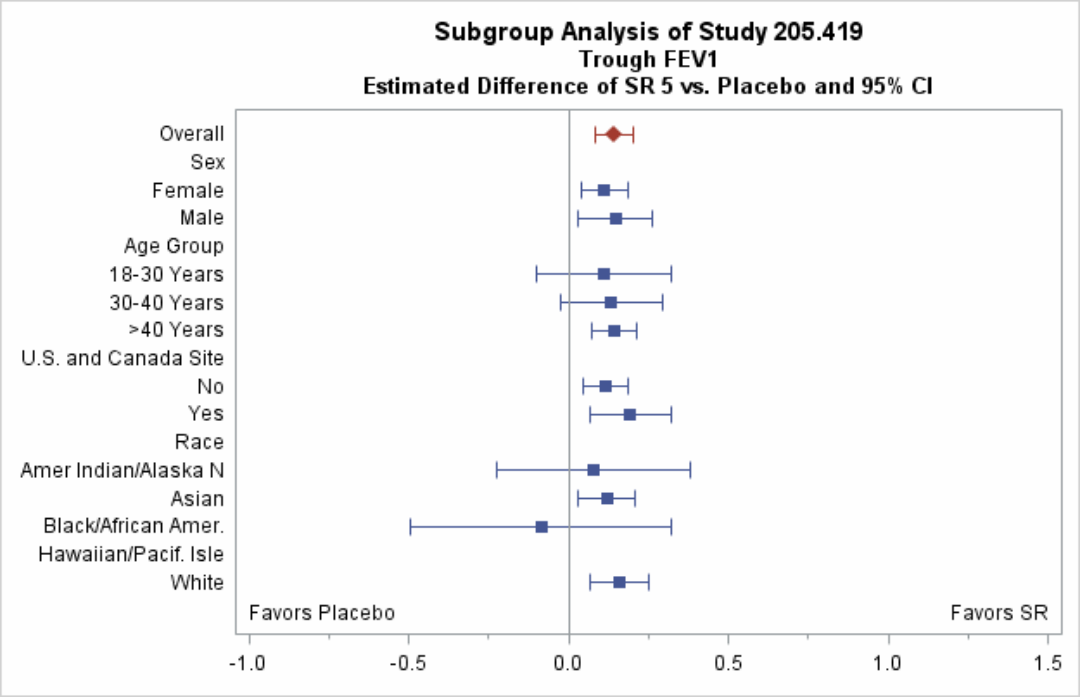
Source: Reviewer Analysis

Figure 14 Subgroup Analysis of Trough FEV_1 (Spiriva Respimat 2.5 mcg)- Study 419



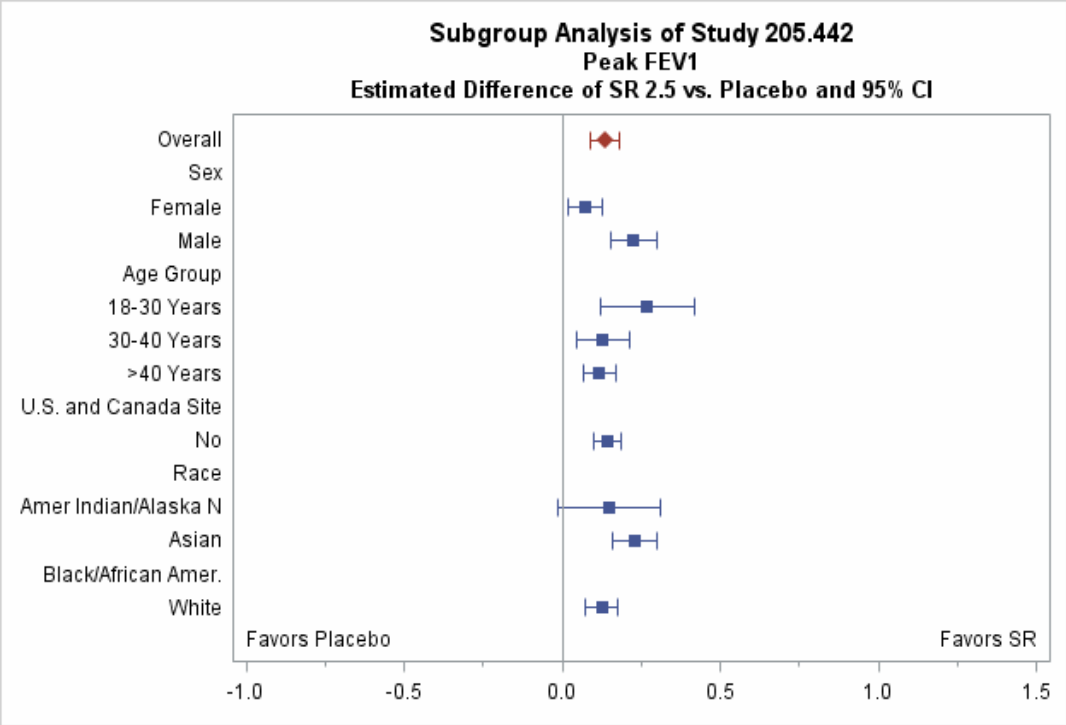
Source: Reviewer Analysis

Figure 15 Subgroup Analysis of Trough FEV_1 (Spiriva Respimat 5 mcg)- Study 419



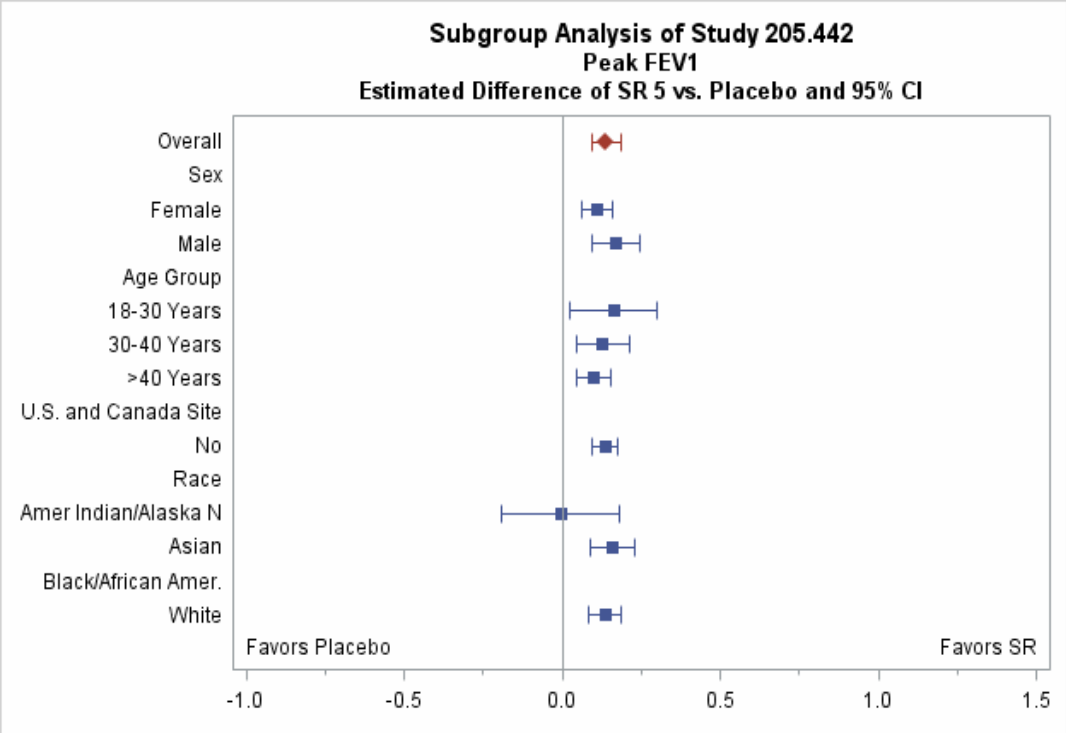
Source: Reviewer Analysis

Figure 16 Subgroup Analysis of Peak FEV_1 (Spiriva Respimat 2.5 mcg)- Study 442



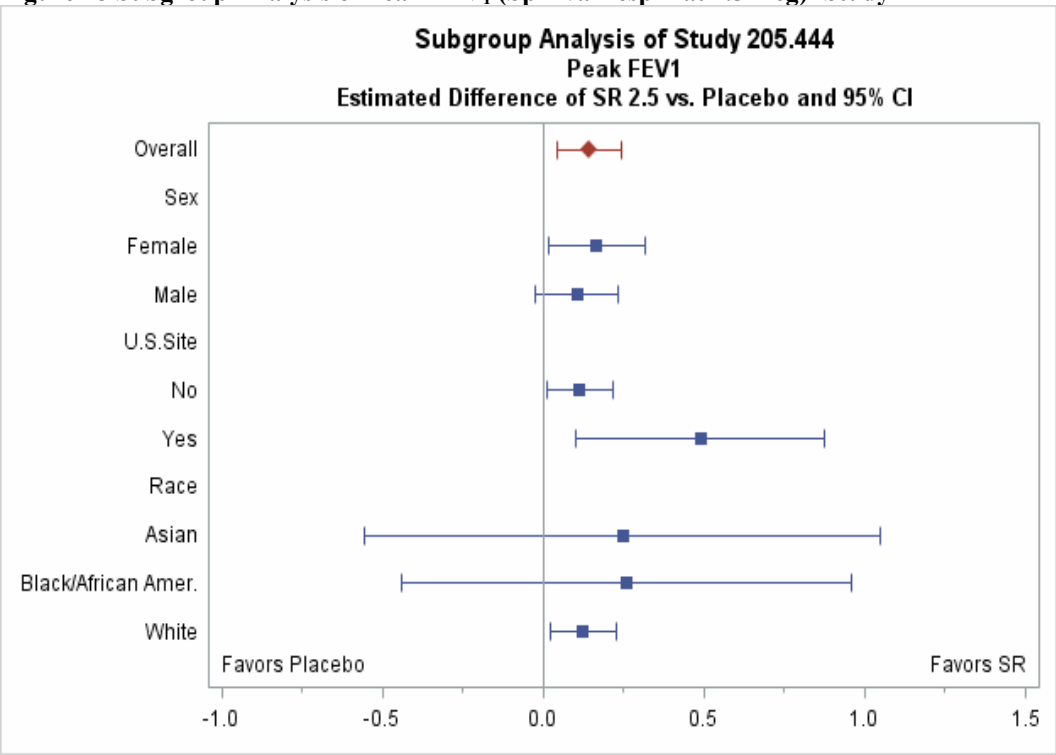
Source: Reviewer Analysis

Figure 17 Subgroup Analysis of Peak FEV_1 (Spiriva Respimat 5 mcg)- Study 442



Source: Reviewer Analysis

Figure 18 Subgroup Analysis of Peak FEV_1 (Spiriva Respimat 2.5 mcg)- Study 444



Source: Reviewer Analysis

Figure 19 Subgroup Analysis of Peak FEV_1 (Spiriva Respimat 5 mcg)- Study 444

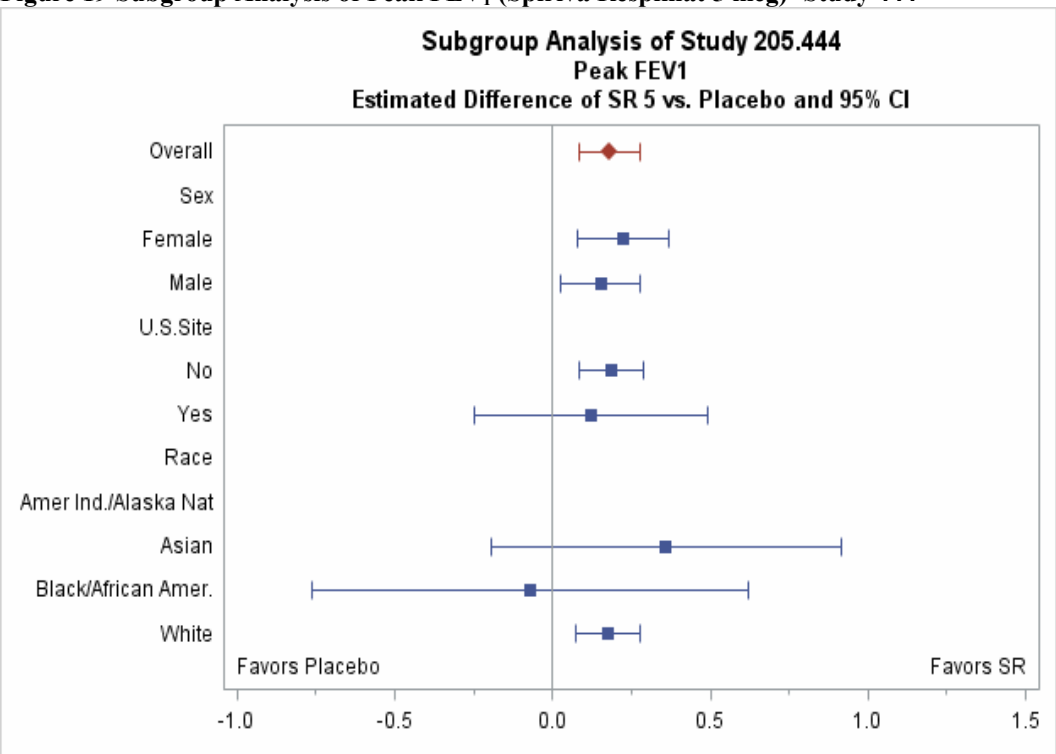


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Figure 20 Subgroup Analysis of Peak FEV1 (Spiriva Respimat 2.5 mcg)- Study 456

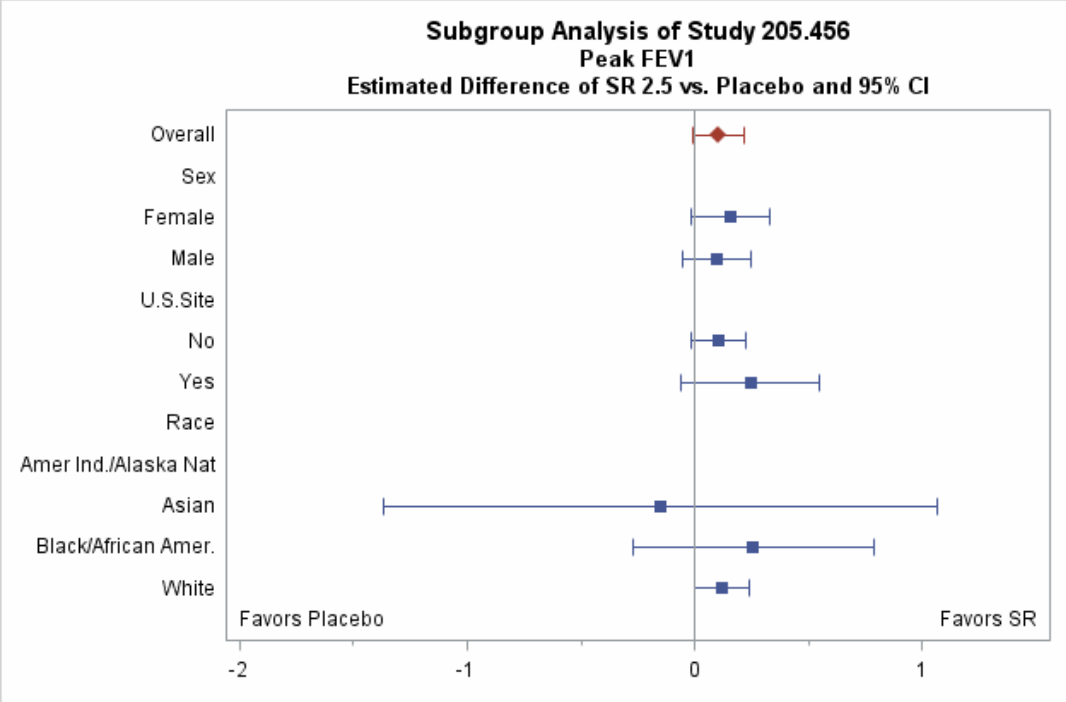

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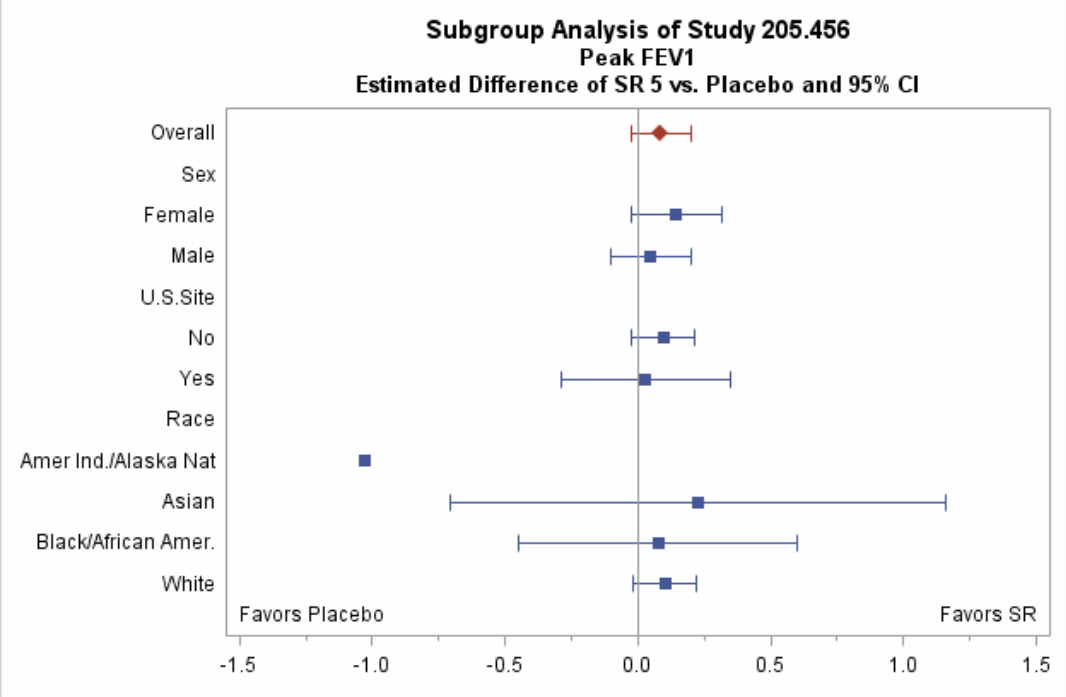
Figure 21 Subgroup Analysis of Peak FEV_1 (Spiriva Respimat 5 mcg)- Study 456



Source: Reveiwer Analysis

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/s/

KIYA HAMILTON
06/10/2015

DAVID M PETULLO
06/10/2015
I concur.