CLINICAL REVIEW

Application Type	NDA
Application Number(s)	207-070
Priority or Standard	Standard
Submit Date(s)	August 15, 2014
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Division / Office	DPARP / ODE II
Reviewer Name(s)	Stacy Chin, MD
Review Completion Date	May 21, 2015
Established Name	Tiotropium Respimat
(Proposed) Trade Name	Spiriva Respimat
Therapeutic Class	long-acting muscarinic antagonist
Applicant	Boeringher Ingelheim
Formulation(s)	Inhalation Solution
Dosing Regimen	(b) (4) µg once daily
Indication(s)	Asthma
Intended Population(s)	12 years and older

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The recommended regulatory action from a clinical perspective is Approval for Spiriva Respimat 2.5 µg once-daily for the long-term, add-on maintenance treatment of asthma in patients 12 years of age and older. (b) (4) Per my review of the risk-benefit assessment, the submitted data support approval of the 2.5 µg dose (b) (4) .

1.2 Risk Benefit Assessment

Based on the data submitted, there is substantial evidence of safety and effectiveness to support the approval of Spiriva Respimat, a long-acting muscarinic antagonist product, 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.

The primary clinical data to support the efficacy of Spiriva Respimat for the proposed indication consisted of a total of seven trials: five in adults and two in adolescents. The bronchodilator activity of Spiriva Respimat in asthma was measured by the absolute peak FEV_1 within 3 hours post-dose (FEV_1 $peak_{(0-3)}$) and trough FEV_1, which were designated as the co-primary or primary/key secondary endpoints in all trials. Although Spiriva Respimat demonstrated a statistically significant difference from placebo on FEV_1 endpoints across trials and in varying asthma severities, the treatment effect size was relatively modest when compared to the response observed with traditional bronchodilators such as beta-agonists. Therefore, asthma exacerbations captured as a secondary endpoint were important to establishing a clinically meaningful benefit for Spiriva Respimat in asthma. In 24- and 48-week long trials, treatment with Spiriva Respimat was associated with a reduced risk of asthma exacerbations compared to treatment with placebo.

For this NDA, (b) (4) . Notably, in phase 3 trials, there was little to no added bronchodilator benefit for the 5 µg dose over the 2.5 µg dose. In fact, in four of five trials where the two doses were compared, the 5 µg dose response was consistently lower. Although the replicate 48-week trials in adults with severe asthma only included Spiriva Respimat 5 µg/day, these trial subjects all had fixed obstructive airway disease to the extent that would fulfill spirometric criteria for the diagnosis of COPD. Because Spiriva Respimat 5 µg/day is already known to be effective in reducing exacerbations in COPD, the generalization of asthma exacerbation data from these trials to broader asthma populations is problematic. However, in trials that evaluated both doses, there was no

significant loss of efficacy between 2.5 µg and 5 µg with regard to reduction in asthma exacerbations.

With respect to safety, there were no major safety concerns or new safety signals identified in the adult or adolescent asthma populations. No deaths were reported in any of the trials, and asthma-related AEs, including serious, non-serious, and those leading to treatment withdrawal, generally occurred more frequently in the placebo groups. Regarding drug-class specific safety concerns, time-adjusted analyses revealed relatively low rates of systemic anticholinergic effects, such as dry mouth, with some evidence of a dose-dependent response between the 2.5 µg and 5 µg doses. Although cardiovascular safety was less of a concern following the completion and review of the TIOSPIR trial in COPD patients, the fact that very few MACE events occurred in the asthma trials with no apparent imbalance between treatment groups was nonetheless reassuring.

In conclusion, the risk-benefit assessment for Spiriva Respimat as a bronchodilator maintenance treatment in patients 12 years of age and older on a background of ICS therapy is favorable. Acknowledging that there are no overt safety issues with the 5 µg dose, an evaluation of the overall safety population revealed fewer asthma-related AEs reported during treatment with 2.5 µg dose compared with the 5 µg dose. Although this difference was not observed in subgroups of adolescent patients or mild asthmatics, the consistency of the efficacy results and trend toward fewer asthma-related AEs favoring the lower 2.5 µg, raises the question of whether or not the higher dose may have a subtle detrimental effect in asthma. Therefore, the risk-benefit profile is most favorable for Spiriva Respimat 2.5 µg/day, which is the recommended dose for approval by this reviewer.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for a postmarketing risk evaluation and mitigation strategy.

1.4 Recommendations for Postmarket Requirements and Commitments

Discussions regarding the Pediatric Study Plan (PSP) for postmarketing PREA studies in asthma patients less than 12 years of age were deferred at the time of this review.

2 Introduction and Regulatory Background

2.1 Product Information

The active component of Spiriva Respimat (SR) is tiotropium bromide monohydrate, a long-acting antimuscarinic (or anticholinergic) drug. The SR drug product consists of an aqueous solution of tiotropium delivered via oral inhalation using the Respimat device. Each actuation from the SR inhaler delivers (b) (4) µg of tiotropium (equivalent to (b) (4) µg

of tiotropium bromide monohydrate) from the mouthpiece. Spiriva Respimat was approved on September 24, 2014, at a dose of 5 µg/day for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), and for reducing COPD exacerbations.

In this NDA, the proposed indication is 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 at the same (b) (4) µg once daily dose (2 actuations of (b) (4) µg).

2.2 Tables of Currently Available Treatments for Proposed Indications

For persistent asthma, the NHBLI NAEPP Expert Panel recommends treatment with a daily controller medication, with first-line therapy being a low-dose inhaled corticosteroid. Alternative and add-on therapies are available; however, use of long-acting beta agonists without a concomitant inhaled corticosteroid is contraindicated due to an increase in asthma-related deaths observed in clinical trials. Currently, there are no anticholinergic agents approved for the treatment of asthma.

Table 1. Currently Available Therapies for the Maintenance Treatment of Asthma

Drug Class	Generic Name	Brand Name
Inhaled corticosteroids	Fluticasone furoate DPI	Arnuity Ellipta
	Beclomethasone diproprionate HFA	QVAR
	Budesonide DPI and respules	Pulmicort
	Fluticasone proprionate HFA and Diskus	Flovent
	Mometasone DPI and HFA	Asmanex
	Ciclesonide HFA	Alvesco
Long-acting beta-agonists	Formoterol fumarate capsule	Foradil
	Salmeterol Diskus	Serevent
Combination inhaled corticosteroid/long-acting beta-agonist (ICS/LABA)	Budesonide/Formoterol HFA	Symbicort
	Fluticasone/Salmeterol HFA and Diskus	Advair
	Mometasone/Formoterol HFA	Dulera
	Fluticasone furoate/Vilanterol	Breo Ellipta
Immunomodulators	Omalizumab (Anti-IgE mAb)	Xolair
Leukotriene modifiers	Montelukast	Singulair
	Zafirlukast	Accolate
	Zileuton	Zyflo
Xanthines	Theophylline	multiple

Abbreviations: DPI=dry powder inhaler, HFA=hydrofluoroalkane, mAb=monoclonal antibody

2.3 Availability of Proposed Active Ingredient in the United States

Tiotropium is available in two formulations for the treatment of COPD: an inhalation solution (Spiriva Respimat) and a dry powder for inhalation (Spiriva Handihaler).

2.4 Important Safety Issues With Consideration to Related Drugs

Class effects of anticholinergic drugs include worsening of narrow angle glaucoma, urinary retention, and decreased secretions leading to effects such as dry mouth. In addition, the Agency has historically had concerns with the cardiovascular safety of tiotropium due to an imbalance in mortality observed in clinical development and in meta-analyses published in the medical literature[1]. To address this concern, the Applicant conducted two large, randomized, double-blind clinical trials in COPD patients to evaluate the long-term safety and risk of mortality: the UPLIFT trial comparing Spiriva Handihaler (SHH) to placebo and the TIOSPIR trial comparing SHH to SR. UPLIFT demonstrated no increased mortality risk with SHH compared to placebo. Results from TIOSPIR demonstrated that SR 5 µg was non-inferior (hazard ratio 0.957 [95% CI 0.837, 1.094]) to SHH 18 µg in terms of all-cause mortality, the primary endpoint. Although sub-analyses revealed an increased number of deaths due to myocardial infarction in the SR 5 µg group, this finding was not supported by results for MI-related serious adverse events, major adverse cardiovascular events (MACE), or stroke-related deaths. For further details, refer to the Medical Officer reviews[2] and transcripts from the public meetings held by the Pulmonary Allergy Drug Advisory Committee[3,4].

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A summary of the regulatory interactions with the Sponsor (BI) and key discussion points related to the asthma clinical development program is provided below:

- June 9, 2008, Type B (EOP2) Meeting
  - (b) (4)

[redacted]

[1] Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. JAMA 2008; 300: 1439-50
[2] For NDA 21-395 (S029) dated August 7, 2009 and for NDA 21-936 dated August 28, 2014
[3] http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM198006.pdf
[4] http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM416247.pdf

- (b) (4)

- August 25, 2009, Type C Meeting
  - (b) (4)
  - Since BI is developing Spiriva Respimat as a bronchodilator indicated for maintenance treatment (b) (4), they should consider single dose trials to better characterize dose-ranging effects. BI responded that single doses may not be representative of the multiple dose effect.
  - (b) (4)
  - To support appropriate labeling, BI should include a trial in mild persistent asthmatics; however, these patients do not necessarily have to be controlled on low dose inhaled corticosteroids.
  - Data on adolescent patients would be required for approval. It was recommended to include adolescents in adult trials if feasible.
  - Evaluation of Spiriva Respimat with an alternative controller medication and in patients with mild intermittent asthma may be required at some point.
  - (b) (4)

- December 9, 2013, Type B (pre-NDA) Meeting
  - The determination of efficacy will be based on results from individual trials, although pooling of identical trials within different asthma severities is acceptable.
  - (b) (4)

- (b) (4)
- Spiriva Respimat represents a new class of drug for treatment of asthma; whether a relatively small improvement in trough FEV1 is adequate for approval as a bronchodilator will be review issue.
- The Division recommended conducting 24-hour FEV1 time profiles for the selected dose once daily and one quarter the selected dose twice daily to support the once versus twice daily dosing regimen.

2.6 Other Relevant Background Information

A history of relevant regulatory activity for Spiriva Respimat and Spiriva Handihaler not directly related to the asthma program is provided below:

- September 16, 2008: Complete Response (Not Approvable Action) for initial COPD submission due to safety concerns for increased risk of stroke and mortality
- November 19, 2009: PADAC meeting to discuss safety data from the UPLIFT trial; committee concluded that UPLIFT data were compelling with Spiriva Handihaler demonstrating generally beneficial effects on mortality compared with placebo
- March 24, 2014: Complete Response resubmission for COPD
- August 14, 2014: PADAC meeting to discuss efficacy and safety data, including data from the TIOSPIR trial, for Spiriva Respimat in COPD
- September 24, 2014: Spiriva Respimat approved for COPD

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The NDA was submitted electronically and included complete study reports, appropriate case report forms, and proposed labeling. The submission was appropriately indexed and organized to permit clinical review. Review of the application did not raise any data integrity concerns. With the assistance of the statistical review team, three sites were selected for inspection either because of high enrollment (Sites 4905/49057 and 56001) or large treatment effect (Site 01019). Table 2 lists the sites, principal investigators, and corresponding trials that were inspected.

Table 2. Sites for OSI Inspection

Site # (Name, Address, Phone number, email, fax#)	Protocol ID	Number of Subjects Enrolled	Indication/Primary endpoint and other endpoints for verification
49005 Dr. Olaf Schmidt KPPK GmbH, Lungen-und Bronchialkunde Lungen-und Bronchialheilkunde Emil-Schuller-Str. 29 56068 Koblenz Ph: +49.2612.9675850 Fax: +49.2612.967585222 schmidt@kppk-gmbh.de	205.416	40	- Peak$_{(0-3)}$ and trough FEV_1 (co-primary endpoints) - Time to first asthma exacerbation/severe exacerbation (secondary)
49057 Dr. Olaf Schmidt Emil-Schuller-Str. 29 56068 Koblenz Ph: +49.2612.9675850 Fax: +49.2612.967585222 (b) (6)	205.419	43	- Peak$_{(0-3)}$ and trough FEV_1 (co-primary endpoints)
01019 Dr. Stephen Tilles ASTHMA Inc. 4540 Sand Point Way NE, Suite 100 Seattle, WA 98105	205.418	22	- Peak$_{(0-3)}$ and trough FEV_1 (co-primary endpoints)
56001 Dr. Carlos Quilodran Hospital Gustavo Fricke Alvarez #1532 Vina del Mar 2570017 Chile Ph: +56.322670955 Fax: +56.322385140 (b) (6)	205.444	38	- Peak$_{(0-3)}$ FEV_1 (primary) - Trough FEV_1 (secondary)

While protocol violations were noted to have occurred at Sites 01019 and 56001, none had a significant impact on the reliability of study data or on the efficacy and safety assessments. Therefore, the Office of Scientific Investigations determined that the study data collected at each of the sites appeared reliable in support of the requested indication and that no action was indicated for Site 49005/49057 while voluntary action was indicated for Sites 01019 and 56001. Refer to the Clinical Inspection Summary by Dr. Anthony Orencia for further details.

3.2 Compliance with Good Clinical Practices

The Applicant stated that all clinical studies and trials were conducted in compliance with Good Clinical Practices and submitted a statement certifying that no debarred individuals participated in the conduct of trials included in this NDA. Prior to initiation, each clinical trial protocol and written informed consent form were reviewed and

approved by local Institutional Review Boards (IRB) or Independent Ethics Committees (IEC).

3.3 Financial Disclosures

The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. Nine of the 721 principal investigators and three sub-investigators reported receipt of significant payments from the Applicant; however, these payments do not appear to raise questions about the integrity of the data. Enrollment at any particular site was relatively small compared to the overall number of patients, and no single site or investigator appears to be driving the results.

Table 3. Financial Disclosure Checklist

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of principal investigators identified: 721		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 12		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 12 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐
Number of investigators with certification of due diligence (Form FDA 3454, box 3)		
Is an attachment provided with the reason:	Yes ☒	No ☐

BI performed due diligence, but was unable to certify financial interests for 106 investigators. For 82 of these investigators, the reason for lack of certification was either that the site did not initiate the trial/did not enroll patients or that the investigator did not participate in the trial. For the remainder of investigators, eight sub-investigators had incomplete financial disclosure questionnaires (FDQ), ten sub-investigators did not have FDQs collected, and five sub-investigators and one PI were no longer at the site. Six of the sub-investigators for whom an FDQ was not collected were from the same site in study 205.419; however, this site does not appear to have randomized any subjects.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Chemistry, Manufacturing, and Controls reviewer is currently evaluating the performance of a 1.25 µg/spray Spiriva Respimat product in order to support a (b) (4) dose (2.5 µg once-daily) (b) (4) .

4.2 Clinical Microbiology

No new data was submitted or required because the microbiology data was previously reviewed under the NDA 21-936 for COPD and the formulation and container closure system remain the same.

4.3 Preclinical Pharmacology/Toxicology

No new data was submitted or required as a full toxicology program has already been conducted to support the Spiriva HandiHaler and Spiriva Respimat COPD programs.

4.4 Clinical Pharmacology

The recommendation from the Clinical Pharmacology reviewer is Approval. A brief review of the clinical pharmacology findings and dose ranging/regimen studies for SR in asthma can be found below. For complete details of the phase 2 program, refer to the Clinical Pharmacology review by Dr. Yunzhao Ren.

4.4.1 Mechanism of Action

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

4.4.2 Pharmacodynamics

For the asthma clinical development program, the Applicant conducted three dose-ranging and two dosing-regimen studies, summaries of which are provided in Table 4. Because all studies contained the same “205” prefix, individual studies are referred to by the last 3 digits only. All were randomized, double-blind, crossover studies with a

placebo control (except Study 441). With the exception of Study 341 which included severe asthmatics on background ICS and LABA therapies, the remainder of dose-ranging/regimen studies evaluated patients with moderate asthma on medium-dose ICS therapy, the demographics and baseline characteristics of whom were similar to those in phase 3 trials.

Table 4. Phase 2 Dose-Ranging and Dosing-Regimen Studies

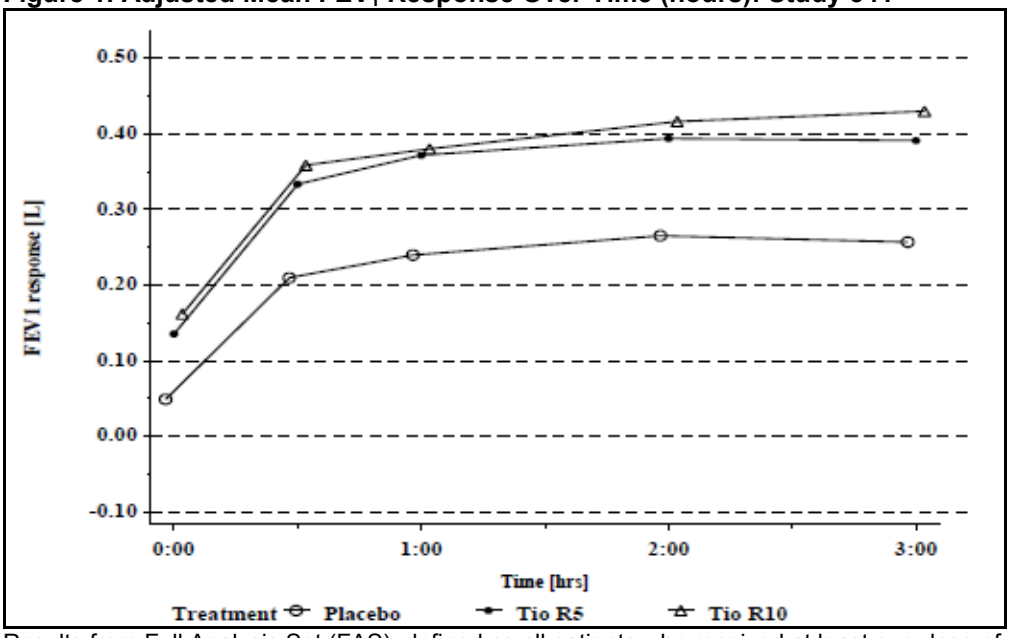
Trial (dates)	Design	Population	Background Medication	Treatment	N	Duration	Primary Endpoint(s)	Sites (countries)
Phase 2 dose-ranging studies								
205.341 *(8/06-11/07)*	R, DB, PC, XO	Adults, severe asthma	High-dose ICS + LABA	SR 5 QD SR 10 QD Placebo	107	8 weeks	FEV_1 $peak_{0-3h}$	16 sites (Denmark, Germany, Netherlands)
205.380 *(11/10-1/12)*	R, DB, PC, XO	Adults, moderate asthma	Medium-dose ICS	SR 5 QD SR 2.5 QD SR 1.25 QD Placebo	149	4 weeks	FEV_1 $peak_{0-3h}$	19 sites (Germany, Austria, Ukraine)
205.424 *(6/10-4/11)*	R, DB, PC, IXO	Adolescents, moderate asthma	Medium-dose ICS	SR 5 QD SR 2.5 QD SR 1.25 QD Placebo	105	4 weeks	FEV_1 $peak_{0-3h}$	19 sites (Germany, Latvia, Lithuania, Slovenia, USA)
Phase 2 dosing-regimen studies								
205.420 *(7/10-8/11)*	R, DB, PC, XO	Adults, moderate asthma	Medium-dose ICS	SR 5 QD SR 2.5 BID Placebo	94	4 weeks	FEV_1 AUC_{0-24h}	15 sites (Czech Republic, Estonia, Latvia, Austria, Germany)
205.441 *(10/12-6/13)*	R, DB, XO	Adults, moderate asthma	Medium-dose ICS	SR 5 QD SR 2.5 BID	98	4 weeks	FEV_1 AUC_{0-24h}	22 sites (Austria, Germany, Hungary, Slovenia)

Abbreviations: R=randomized, DB=double-blind, PC=placebo-controlled, PG=parallel group, XO=crossover, IXO=incomplete crossover, ICS=inhaled corticosteroid, LABA=long-acting beta-agonist, SR=Spiriva Respimat, Sal 50=Salmeterol HFA 50 µg, QD=once daily, BID=twice daily, PEF=peak expiratory flow rate, USA=United States of America
N=randomized subjects
Source: Module 2.7.6, Synopses of Individual Studies

Nominal dose selection

In three dose-ranging studies, the Applicant explored nominal doses ranging from 1.25 µg to 10 µg for SR in asthma. Study 341 was a randomized, double-blind, placebo-controlled 24-week crossover study with 8 week treatment periods that evaluated SR 5 µg and SR 10 µg once-daily in the morning in 107 adults with severe persistent asthma on a background of high-dose ICS and LABA therapies. At the end of each 8-week treatment period, there was an approximate 125-150mL difference in peak FEV_1 within the first 3 hours post-dose (FEV_1 $peak_{(0-3h)}$) with active treatment compared to placebo, but no significant difference between the 5 and 10 µg doses (Figure 1). Similar findings were observed in trough FEV_1 response between active treatment groups and placebo.

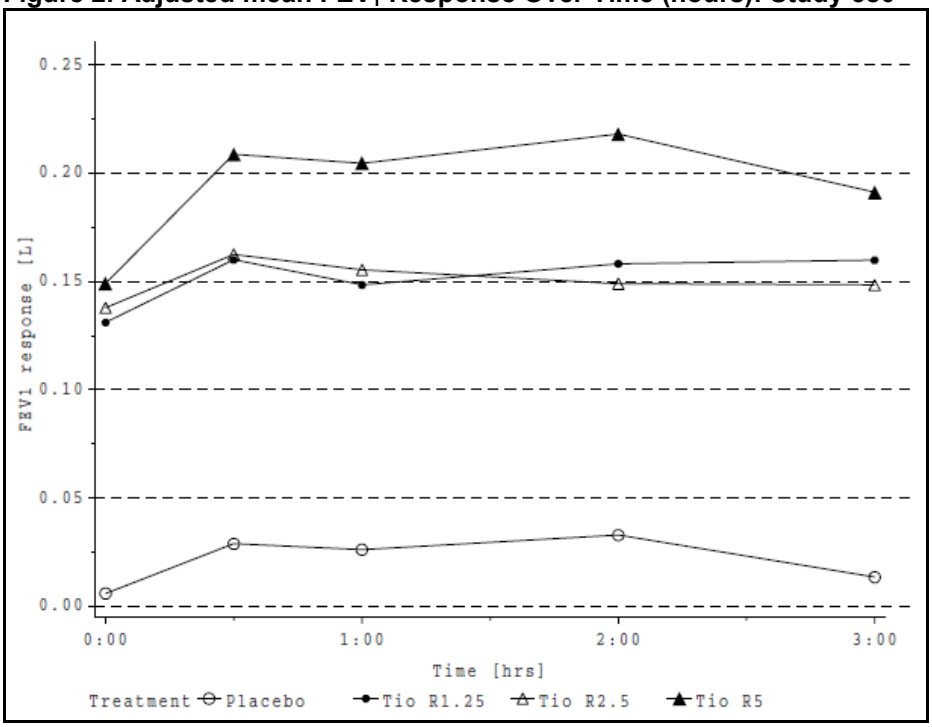
Figure 1. Adjusted Mean FEV_1 Response Over Time (hours): Study 341



Results from Full Analysis Set (FAS), defined as all patients who received at least one dose of study medication and had at least one efficacy measurement.
Means adjusted for pooled center, patient within pooled center, and period.
Source: CSR 205.341, Figure 11.4.1.2:1

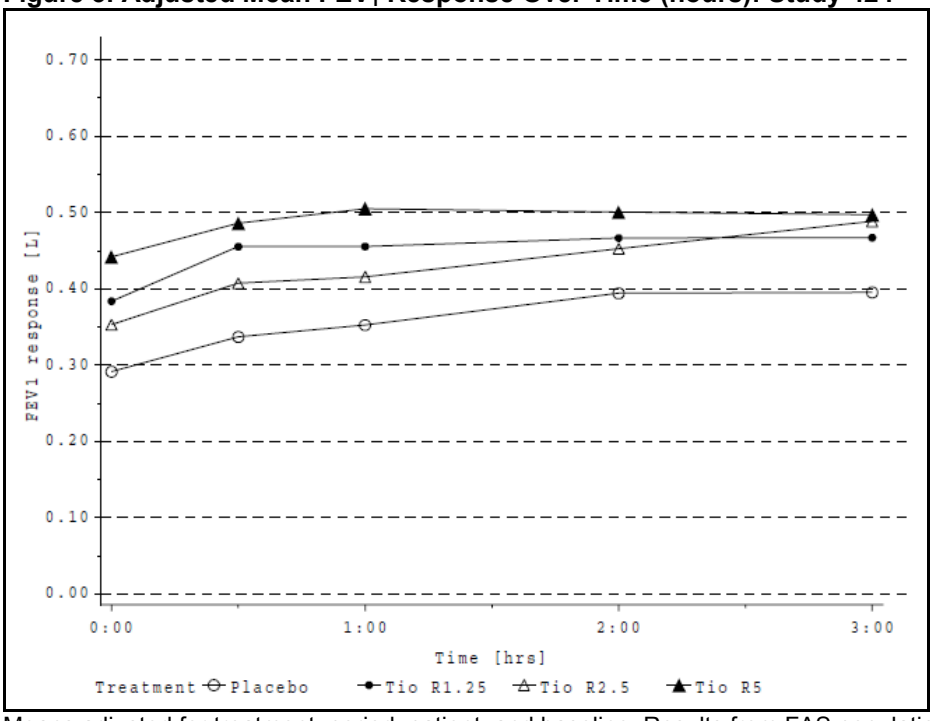
Because the 10 µg dose had similar treatment effects on FEV_1 with more anticholinergic side effects such as dry mouth, the Applicant evaluated lower doses in Studies 380 and 424. Study 380 was a randomized, double-blind, placebo-controlled, 16-week crossover study that evaluated three doses of SR (1.25, 2.5, and 5 µg) once daily in the evening in 149 adults with moderate asthma. Similarly, Study 424 evaluated the same three doses of SR administered once daily in the evening, but was an incomplete crossover design of 12 weeks duration in 105 adolescents (12-17 years of age) with moderate asthma. The adjusted mean FEV_1 response over 3 hours post-dose after 4 weeks of treatment from each study is displayed graphically in Figure 2 and Figure 3. In both studies, the primary analysis demonstrated the largest treatment difference between SR 5 and placebo for the FEV_1 $peak_{(0\text{-}3h)}$ response after 4 weeks of treatment. Although the lower doses had a lesser effect on post-dose FEV_1, there was no clear dose-response relationship between the 1.25 and 2.5 µg doses. Similar trends were observed for the trough FEV_1 response.

Figure 2. Adjusted mean FEV_1 Response Over Time (hours): Study 380



Means adjusted for treatment, period, patient, and study baseline. Results from FAS population.
Source: CSR 205.380, Figure 11.4.1.2.1:1

Figure 3. Adjusted Mean FEV_1 Response Over Time (hours): Study 424

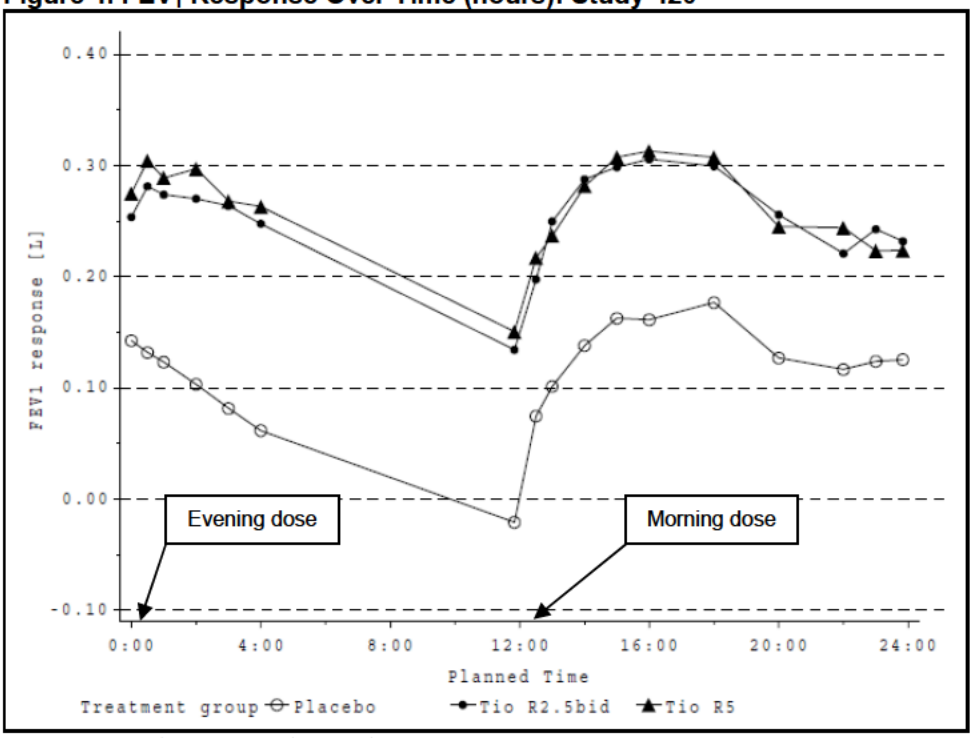


Means adjusted for treatment, period, patient, and baseline. Results from FAS population.
Source: CSR 205.424, Figure 11.4.1.2.1:1

Dosing frequency

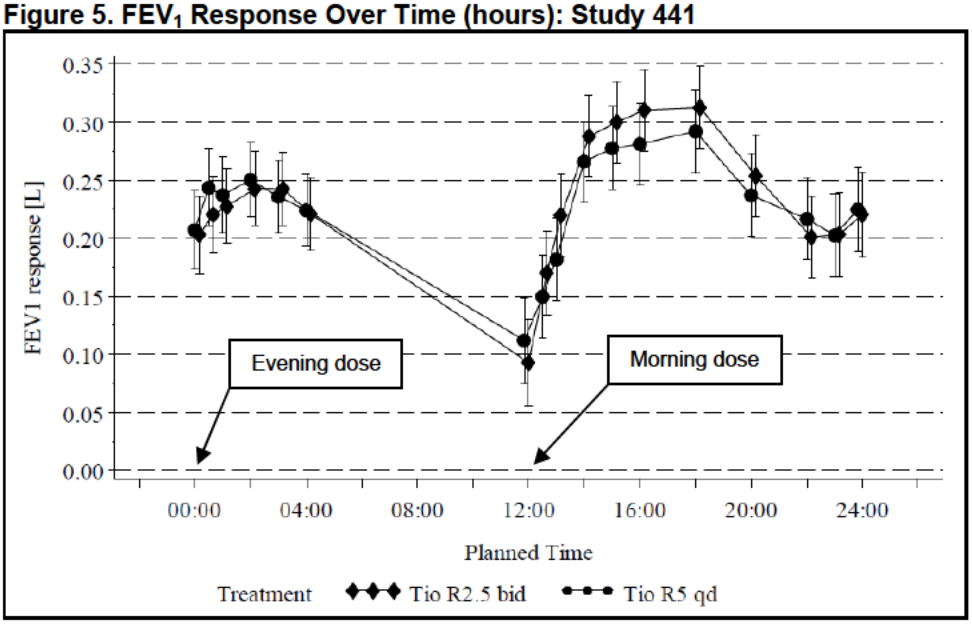
Once versus twice-daily dosing was evaluated in studies 420 and 441, both of which were randomized, double-blind, crossover studies in moderate asthmatic adults. Study 420 included a placebo control, while study 441 did not. Both studies evaluated the 24-hour bronchodilator effects of SR 5 µg once daily in the evening compared to SR 2.5 µg administered twice daily in the morning and evening after 4 weeks of treatment. The adjusted mean FEV_1 $AUC_{0\text{-}24h}$ response was significantly different between both active treatments and placebo with no substantial difference between the two SR dosing regimens. A graphical representation of the FEV_1 24-hour time profile curves from each study are shown in Figure 4 and Figure 5. The increase in FEV_1 occurring at the 12:00 hour time point, regardless of once versus twice daily dosing, is likely explained by the physiologic increase in morning lung function.

Figure 4. FEV_1 Response Over Time (hours): Study 420



Time represents hours post-inhalation of evening dose
Source: CSR 205.420, Figure 11.4.1.2.1:1

Figure 5. FEV_1 Response Over Time (hours): Study 441



Time represents hours post-inhalation of evening dose
Source: CSR 205.441, Figure 11.4.1.2.1:1

In summary, results from the five dose-ranging/regimen studies failed to demonstrate dose separation between the 2.5 and 5 µg doses, but provided adequate support for selecting SR 2.5 µg and SR 5 µg doses as well as the once-daily dosing regimen for phase 3 trials. However, it should be noted that the asthma dose-ranging studies were conducted either concurrently with or following the major phase 3 trials. Therefore, the phase 2 study results must be interpreted within the context of the drug development timeline and integrated with the overall results from the larger and longer phase 3 trials, which can also be considered dose-ranging in themselves.

4.4.3 Pharmacokinetics

Absorption:

Following inhalation of tiotropium bromide, urinary excretion data suggests that approximately 33% of the inhaled dose reaches the systemic circulation. Oral solutions of tiotropium have an absolute bioavailability of 2-3%; therefore, food is not expected to influence the absorption. At steady state, maximum tiotropium plasma concentrations were observed approximately 5 minutes after inhalation in asthma patients.

Distribution:

The drug has a plasma protein binding of 72% and shows a volume of distribution of 32 L/kg after an intravenous dose to young healthy volunteers. Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung. Studies in rats have shown that tiotropium does not penetrate the blood-brain barrier.

Metabolism:
The extent of metabolism appears to be small, evident from a urinary excretion of 74% of unchanged substance after an intravenous dose. Tiotropium, an ester, is non-enzymatically cleaved to the alcohol N-methylscopine and dithienylglycolic acid, neither of which binds to muscarinic receptors.

In vitro experiments with human liver microsomes and human hepatocytes suggest that a fraction of the administered dose (~25%) is metabolized by cytochrome P450-dependent oxidation and subsequent glutathione conjugation to a variety of Phase II metabolites. This enzymatic pathway can be inhibited by CYP450 2D6 and 3A4 inhibitors, such as quinidine, ketoconazole, and gestodene. *In vitro* studies using human liver microsomes showed that tiotropium in supra-therapeutic concentrations does not inhibit CYP450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4.

Elimination:
At steady state following 2.5 µg once daily inhalation, the effective half-life of tiotropium was approximately 1.5 days in asthma patients. Total clearance was 880 mL/min after an intravenous dose in young healthy volunteers. In asthma patients, pharmacokinetic steady-state was reached by day 7 with no accumulation thereafter. At steady state, 24-hour urinary excretion is 18.6% (0.93 µg) and 12.8% (0.32 µg) of the dose in patients with COPD (5 µg once daily) and asthma (2.5 µg once daily), respectively. The renal clearance of tiotropium exceeds the creatinine clearance, indicating secretion into the urine.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

All of the trials conducted in the asthma development program for SR are summarized in Table 5. Because all studies/trials included the same prefix of 205, this review refers to an individual study/trial by the last 3 digits only. In the phase 2 program, there were five dose-ranging/regimen studies in the phase 2 program: 341, 380, 424, 420, and 441. The results from these studies formed the basis for dose selection in phase 3 trials and were discussed in Section 4.4.2. The information to support the efficacy and safety of SR for the maintenance treatment of asthma on a background of ICS therapy is derived primarily from seven trials (416, 417, 418, 419, 442, 444, and 456). The protocols for the efficacy and safety trials are reviewed in Section 5 while efficacy and safety results are discussed in Sections 6 and 7, respectively. Additional safety data is provided by a long-term safety trial conducted in Japan (464) and a parallel-group phase 2 study (342), which are reviewed as part of the pooled safety database in Section 7.

Table 5. Phase 2 and 3 Studies/Trials

Trial (dates)	Design	Population	Background Medication	Treatment	N	Duration	Primary Endpoint(s)	Sites (countries)
Phase 2 dose-ranging studies								
205.341 *(8/06-11/07)*	R, DB, PC, XO	Adults, severe asthma	High-dose ICS + LABA	SR 5 QD SR10 QD Placebo	107	8 weeks	FEV_1 $peak_{0-3h}$	16 sites (Denmark, Germany, Netherlands)
205.380 *(11/10-1/12)*	R, DB, PC, XO	Adults, moderate asthma	Medium-dose ICS	SR 5 QD SR 2.5 QD SR 1.25 QD Placebo	149	4 weeks	FEV_1 $peak_{0-3h}$	19 sites (Germany, Austria, Ukraine)
205.424 *(6/10-4/11)*	R, DB, PC, IXO	Adolescents, moderate asthma	Medium-dose ICS	SR 5 QD SR 2.5 QD SR 1.25 QD Placebo	105	4 weeks	FEV_1 $peak_{0-3h}$	19 sites (Germany, Latvia, Lithuania, Slovenia, USA)
Phase 2 dosing-regimen studies								
205.420 *(7/10-8/11)*	R, DB, PC, XO	Adults, moderate asthma	Medium-dose ICS	SR 5 QD SR 2.5 BID Placebo	94	4 weeks	FEV_1 AUC_{0-24h}	15 sites (Czech Republic, Estonia, Latvia, Austria, Germany)
205.441 *(10/12-6/13)*	R, DB, XO	Adults, moderate asthma	Medium-dose ICS	SR 5 QD SR 2.5 BID	98	4 weeks	FEV_1 AUC_{0-24h}	22 sites (Austria, Germany, Hungary, Slovenia)
Phase 2 special population study								
205.342 *(7/06-9/08)*	R, DB, PC, PG, AC	Adults, moderate asthma with B16-Arg/Arg Homozygous for arginine at 16th amino acid position of β_2-adrenergic receptor	Medium-dose ICS ± LABA	SR 5 Sal 50 BID Placebo	128 134 126	16 weeks	mean weekly morning pre-dose PEF	113 sites (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Italy, Russia, Slovakia, South Africa, Spain, Turkey, UK)
Phase 3 efficacy and safety trials in adults								
205.416 *(10/08-7/11)*	R, DB, PC, PG	Adults, severe asthma	High-dose ICS + LABA	SR 5 QD Placebo	237 222	48 weeks	FEV_1 $peak_{0-3h}$ Trough FEV_1 *Time to 1st severe exacerbation	73 sites (Australia, Canada, Denmark, Germany, Italy, Japan, Netherlands, Russia, Serbia, South Africa, Turkey, Ukraine, UK, USA)
205.417 *(11/08-7/11)*	R, DB, PC, PG	Adults, severe asthma	High-dose ICS + LABA	SR 5 QD Placebo	219 234	48 weeks	FEV_1 $peak_{0-3h}$ Trough FEV_1 *Time to 1st	75 sites (Australia, Canada, Denmark,

Trial (dates)	Design	Population	Background Medication	Treatment	N	Duration	Primary Endpoint(s)	Sites (countries)
							severe exacerbation	Germany, Italy, Jan, Netherlands, New Zealand, Russia, Serbia, South Africa, Turkey, Ukraine, UK, USA)
205.418 *(9/10-11/12)*	R, DB, PC, PG	Adults, moderate asthma	Medium-dose ICS	SR 5 QD SR 2.5 QD Sal 50 BID Placebo	265 262 275 269	24 weeks	FEV_1 $peak_{0-3h}$ Trough FEV_1 *ACQ responder rate	114 sites (Latvia, Poland, Russia, Brazil, China, Guatemala, India, Japan, Mexico, Peru, USA)
205.419 *(8/10-11/12)*	R, DB, PC, PG	Adults, moderate asthma	Medium-dose ICS	SR 5 QD SR 2.5 QD Sal 50 BID Placebo	254 258 266 259	24 weeks	FEV_1 $peak_{0-3h}$ Trough FEV_1 *ACQ responder rate	124 sites (Brazil, China, Columbia, Germany, India, Japan, Mexico, Peru, Poland, Romania, USA)
205.442 *(4/11-4/12)*	R, DB, PC, PG	Adults, mild asthma	Low-dose ICS	SR 5 QD SR 2.5 QD Placebo	155 154 156	12 weeks	FEV_1 $peak_{0-3h}$ **Trough FEV_1	65 sites (Argentina, Austria, Croatia, Estonia, Guatemala, Hungary, India, Italy, Korea, Latvia, Poland, Slovakia)
Phase 3 efficacy and safety trials in adolescents								
205.444 *(1/11-12/13)*	R, DB, PC, PG	Adolescents, moderate asthma	Medium-dose ICS	SR 5 QD SR 2.5 QD Placebo	135 125 138	48 weeks	FEV_1 $peak_{0-3h}$ **Trough FEV_1	65 sites (Germany, Spain, Hungary, Italy, Slovakia, Latvia, Ukraine, Russia, Korea, Mexico, Chile, USA)
205.456 *(1/11-10/13)*	R, DB, PC, PG	Adolescents, severe asthma	High-dose ICS + 1 controller OR medium-dose ICS + 2	SR 5 QD SR 2.5 QD Placebo	130 127 135	12 weeks	FEV_1 $peak_{0-3h}$ **Trough FEV_1	68 sites (Argentina, Australia, Bulgaria, Germany, Guatemala,

Trial (dates)	Design	Population	Background Medication	Treatment	N	Duration	Primary Endpoint(s)	Sites (countries)
			controllers					Hungary, Israel, Latvia, Mexico, Philippines, Portugal, South Africa, Ukraine, USA)
Phase 3 long-term safety trial								
205.464 *(4/11-4/13)*	R, DB, PC, PG	Adults, moderate to severe asthma	Medium-dose ICS ± LABA	SR 5 QD SR 2.5 QD Placebo	114 114 57	52 weeks	**Trough FEV_1	54 sites (Japan)

Abbreviations: R=randomized, DB=double-blind, PC=placebo-controlled, PG=parallel group, XO=crossover, IXO=incomplete crossover, ICS=inhaled corticosteroid, LABA=long-acting beta-agonist, SR=Spiriva Respimat, Sal 50=Salmeterol HFA 50 µg, QD=once daily, BID=twice daily, PEF=peak expiratory flow rate, UK=United Kingdom, USA=United States of America
N=randomized subjects
*Primary endpoint for pooled analysis
**Key secondary endpoint
Source: Module 2.7.6, Synopses of Individual Studies

5.2 Review Strategy

This review focuses on the phase 3 trials which are clinically relevant to the demonstration of efficacy and safety of SR for the treatment of asthma. The dose-ranging and regimen studies are summarized in Section 4.4.2 and reviewed in detail in the Clinical Pharmacology review by Dr. Yunzhao Ren. The protocols of the confirmatory trials are described in Section 5.3 with efficacy and safety results reviewed in Sections 6 and 7, respectively.

5.3 Discussion of Individual Studies/Clinical Trials

Each trial protocol is discussed individually below with the exception of replicate trials, 416/417 and 418/419, which are discussed jointly. Trials 416/417 are described in greatest detail while only differences in the protocols are noted for the remainder of trials.

Trials 205.416 and 205.417

Title	A Phase III randomized, double-blind, placebo-controlled, parallel-group trial to evaluate efficacy and safety of tiotropium inhalation solution delivered via Respimat inhaler (5 µg/day) over 48 weeks as add-on controller therapy on top of usual care in patients with severe persistent asthma
Trial #	**205.416**
Study dates	Study initiated: October 30, 2008 Study completed: July 25, 2011 Final study report: August 13, 2012 (revised 4/25/13)
Sites	73 clinical study sites in 14 countries (Australia, Canada, Denmark, Germany, Italy, Japan, The Netherlands, Russia, Serbia, South Africa, Turkey, Ukraine, United

	Kingdom, and the United States)
Trial #	**205.417**
Study dates	Study initiated: November 3, 2008 Study completed: July 22, 2011 Final study report: August 13, 2012 (revised 4/25/13)
Sites	75 clinical study sties in 15 countries (Australia, Canada, Denmark, Germany, Italy, Japan, The Netherlands, New Zealand, Russia, Serbia, South Africa, Turkey, Ukraine, United Kingdom, and the United States)

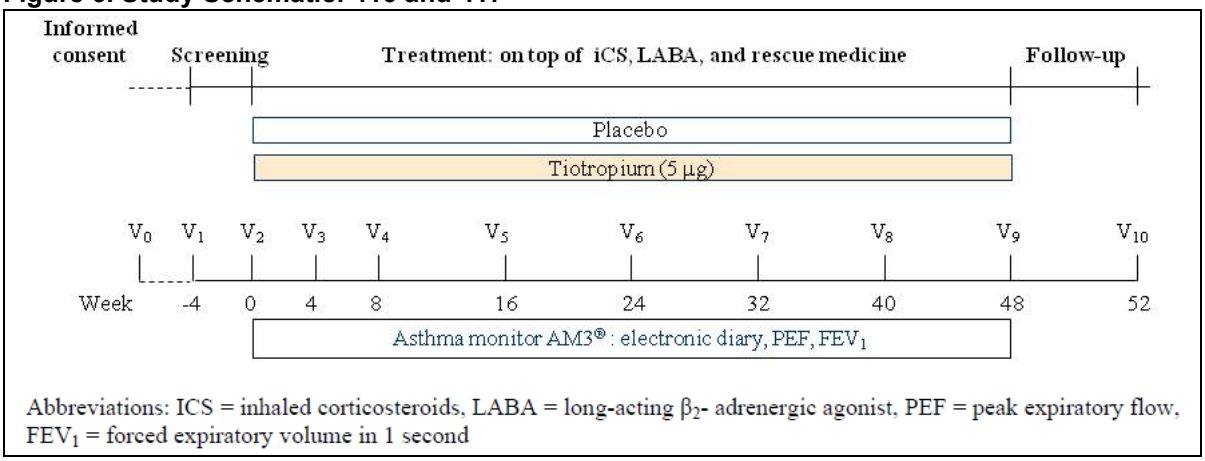
Objectives

The primary objective of each trial was to evaluate the long term efficacy of tiotropium over placebo on top of usual care in patients with severe persistent asthma as determined by pulmonary function testing and by effects on asthma exacerbations, quality of life, asthma control, and health care utilization. The secondary objective of each trial was to compare the long term safety of tiotropium with placebo in this patient population.

Study Design

The replicate trials were multi-center, randomized, double-blind, placebo-controlled, parallel-group in design and evaluated the efficacy and safety of SR 5 µg compared to placebo in addition to usual care in severe asthmatic adults. After providing informed consent and undergoing an initial screening visit, patients entered a 4-week screening period. At Visit 2, eligible patients who met entry criteria following the screening period were randomized 1:1 to blinded treatment with either SR 5 µg or placebo for 48 weeks. Study medication was administered as two puffs once daily in the morning via the Respimat inhaler. Patients continued their usual background medication which must have included high-dose inhaled corticosteroids (ICS) and long-acting β2-adrenergic agonists (LABAs). A short-acting β2-adrenergic agonist, salbutamol, was provided as rescue medication for use as needed during the trial. Clinic visits occurred every 4 to 8 weeks during the trial and included a follow-up visit 4 weeks after the treatment period (Figure 6). Although changes in asthma medication during the trial were not recommended, patients were not prematurely withdrawn if a stable change of asthma maintenance therapy was required.

Figure 6. Study Schematic: 416 and 417



Source: 205.416 CSR, Figure 9.1:1, p45

Patient Population

A minimum of 300 patients were to be randomized in the trial with each site expected to enter a minimum of 6-8 patients. Following the planned interim analysis, the independent data monitoring committee (IDMC) could recommend adjusting the sample size to 400 patients (200 per treatment group) based on the observed hazard ratio on severe asthma exacerbations.

Key Inclusion Criteria

1. Males or females aged 18 to 75 years
2. Minimum 5-year history of asthma at the time of enrollment. The diagnosis must have been previously confirmed and documented by at least one of the following:
    a. An increased hyperresponsiveness to histamine, methacholine, mannitol, or exercise challenge
    b. A positive trial of glucocorticosteroids or bronchodilator reversibility to a β2-adrenergic drug that resulted in an increase in either FEV_1 by ≥ 12% and ≥ 200 mL from baseline or PEF by ≥ 20%
    c. Diurnal PEF variability of ≥ 10% with two measurements/day or of ≥ 20% with more than two measurements/day (Diurnal PEF variability was defined as the difference between the maximum and minimum PEF value for the day expressed as percentage of the mean daily PEF value and averaged over 7 to 14 days)
    d. Post-bronchodilator (30 minutes after 4 puffs of 100 µg salbutamol/albuterol) reversibility, defined as an increase in FEV_1 by ≥ 12% and ≥ 200 mL from baseline (could have been performed at Visit 1)
3. Asthma diagnosed prior to age 40
4. Severe persistent asthma that was symptomatic despite treatment with high, stable doses of inhaled corticosteroids and a long-acting beta adrenergic agonist

5. Treatment with a stable, high-dose of ICS (Table 6) and LABA for at least 4 weeks before screening (Visit 1). Additional concomitant asthma medications were allowed in stable doses (Table 7).
6. Symptomatic at screening (Visits 1 and 2), defined as ACQ mean score of ≥1.5
7. One or more asthma exacerbations in the past year (based on patient-reported need for urgent care due to asthma symptoms requiring an addition or increased dose of systemic corticosteroids)
8. Post-bronchodilator (i.e., 30 minutes after 4 puffs of 100 µg salbutamol/albuterol) FEV_1 ≤ 80% predicted and FEV_1 ≤ 70% of FVC at Visit 1
9. Variation of absolute pre-bronchodilator and pre-dose FEV_1 values within ± 30% between Visits 1 and 2
10. Never-smokers or ex-smokers who stopped smoking at ≥ 1 year prior to enrollment with a smoking history of < 10 pack years [Pack years = (# cigarettes per day/20) x years smoking]

Table 6. Definition of High-dose Inhaled Corticosteroids

Substance	High dose [µg/day]
Beclometasone dipropionate	≥1000
Budesonide	≥800
Ciclesonide	≥320
Flunisolide	≥2000
Fluticasone	≥500
Mometasone furoate	≥800
Triamcinolone acetonide	≥2000

Source: 205.416 CSR, Table 9.3.1:1, p48

Key Exclusion Criteria

1. Significant disease other than asthma that in the opinion of the investigator may have put the patient at risk, influenced the results of the trial, or raised concern regarding patient's ability to participate
2. Clinically relevant abnormal screening hematology or chemistry labs
3. Recent myocardial infarction (within the previous 6 months)
4. Hospitalization for cardiac failure during the past year
5. Unstable or life-threatening cardiac arrhythmia requiring intervention or change in drug therapy within the past year
6. Malignancy treated by resection, radiation, or chemotherapy within the past 5 years; basal cell carcinoma allowed
7. Lung disease other than asthma (e.g., COPD)
8. Active tuberculosis
9. Alcohol or drug abuse within the past two years
10. Previous thoracotomy with pulmonary resection
11. Participation in pulmonary rehabilitation program currently or within 6 weeks prior to screening (Visit 1)
12. Oral corticosteroid use at doses > 5 mg daily or > 10 mg every other day of prednisolone or prednisolone equivalent

13. Pregnancy or lactation
14. Women of childbearing potential not using a highly effective method of contraception.
15. Asthma exacerbation or respiratory tract infection within 4 weeks of screening (Visit 1) or during the 4-week screening period; for events that occurred during the screening period, patients could have been randomized 4 weeks following recovery
16. Narrow-angle glaucoma
17. Treatment with tiotropium within 4 weeks of screening (Visit 1) or during the screening period
18. Treatment with disallowed medications (Table 7)

Reviewer Comment: Inclusion criterion #8 is also the spirometric diagnostic criterion for COPD outlined in the 2015 GOLD report.

Concomitant Medications
The following table lists the medications that were permitted or prohibited prior to and during the trials.

Table 7. Overview of Permitted and Prohibited Medications: Trials 416 and 417

Drug Class	Sub-class	Prior to trial	Trial Period		
			Screening Period	Treatment Period	Follow up Period
Corticosteroids	Inhaled corticosteroids (high dose)[1]	required	required	required	required
	Oral corticosteroids[1] [≤ 5 mg prednisolone per day or ≤ 10 mg prednisolone every second day (or prednisolone equivalent)]	permitted	permitted	permitted	permitted
Beta-adrenergics / Beta-blockers	Inhaled rapid-acting beta-adrenergics[2]	permitted	**rescue**	**rescue**	**rescue**
	Inhaled long-acting beta-adrenergics[1,2]	required	required	required	required
	Oral beta-adrenergics[3]	not permitted	not permitted	not permitted	not permitted
	Beta blockers[3, 4]	not permitted	not permitted	not permitted	not permitted
Anticholinergics	Short-acting anticholinergics[2] (inhalation aerosol and nasal spray)	permitted	permitted	not permitted	permitted
	Long-acting anticholinergics[3]	not permitted	not permitted	**Trial medication**	not permitted

Miscellaneous	Other investigational drugs[5]	not permitted	not permitted	not permitted	not permitted
	Cromolyn sodium / nedocromil sodium[1]	permitted	permitted	permitted	permitted
	Antihistamines[1]	permitted	permitted	permitted	permitted
	Methylxanthines[1,2]	permitted	permitted	permitted	permitted
	Mucolytics[1]	permitted	permitted	permitted	permitted
	Leukotriene modifiers[1]	permitted	permitted	permitted	permitted
	Anti-IgE treatment (e.g. Omalizumab)[1]	permitted	permitted	permitted	permitted
	'Experimental', non-approved asthma medications (e.g TNF-alpha blockers)[3]	not permitted	not permitted	not permitted	not permitted

1 to be stabilized for four weeks prior to Visit 1 and throughout the trial
2 washout to be obeyed prior to Visits with pulmonary function testing
3 washout of at least four weeks prior to Visit 1
4 Topical cardio-selective beta-blocker eye medications for treatment of non-narrow angle glaucoma are allowed
5 washout of at least four weeks or six half lives (whichever is greater) prior to Visit 1

Source: 205.416 Protocol, Table 4.2: 1, p45

Treatments

- Tiotropium: 5 µg daily delivered as 2 puffs of 2.5 µg once every morning via the Respimat inhaler
- Placebo: 2 puffs once every morning delivered via the Respimat inhaler

Subjects were instructed to inhale study medication once daily each morning at the same time (± 30 minutes) between 7am and 10am and within 10 minutes after the inhalation of their usual asthma therapy. Patients recorded the administration of each dose of trial medication in their electronic diary; patients who missed a dose were instructed to take the next dose at the next scheduled time. On clinic visit days, patients were to withhold their morning dose of trial medication and their usual asthma medication, both of which would be administered in the clinic after the pre-dose pulmonary function test.

Open-label salbutamol (albuterol) HFA MDI inhalation aerosol (100 µg per actuation) was supplied for the assessment of post-bronchodilator FEV_1 at Visit 1 and for rescue use during the screening, treatment, and follow-up periods. Rescue medication was allowed at any point during the trial; however if administered before or during a clinic visit day, the visit was either re-scheduled or discontinued without the patient completing the remainder of the pulmonary function testing. Patients were instructed to record the number of inhalations of rescue medication used during the daytime and nighttime in the electronic diary of the Asthma Monitor (AM3) device.

Treatment compliance was assessed at each clinic visit through a review of the electronic diaries and the used trial and rescue medications returned to clinic.

Efficacy Variables

Pulmonary Function Testing Procedures

At screening (Visit 1), pulmonary function testing was performed 10 minutes prior to and 30 minutes after inhalation of 4 puffs of 100 µg salbutamol. Predicted FEV_1 values were calculated for patients according to the European Community for Steel and Coal (ECSC) reference equations:

Males
FEV_1 predicted (L)=4.3 x (height (inches)/39.37) – 0.029 x age (years) – 2.49
FEV_1 predicted (L)=4.3 x (height (meters)) – 0.029 x age (years) – 2.49

Females
FEV_1 predicted (L)=3.95 x (height (inches)/39.37) – 0.025 x age (years) – 2.60
FEV_1 predicted (L)=3.95 x (height (meters)) – 0.025 x age (years) – 2.60

Patients 18-25 years of age had predicted FEV_1 calculated using age 25.

Reviewer Comment: The ECSC reference equations tend to result in lower percent predicted FEV_1 (i.e., predicts higher FEV_1 for given age, sex, and height) compared to other reference equations.

At Visit 2, baseline pulmonary function testing (FEV_1 and FVC) was performed 10 minutes pre-dose followed by administration of the patient's usual asthma therapy and then the first dose of trial medication within 10 minutes. Pulmonary function testing was subsequently performed at 30 minutes, 1 hour, 2 hours, and 3 hours after inhalation of the trial medication. Pulmonary function testing was performed according to the same schedule at Visits 3-9. The end of the 2nd inhalation of trial medication from the Respimat inhaler was regarded as time point zero for pulmonary function testing. PFTs were performed in triplicate with the highest value recorded; however, the PFT time point recorded was derived from the time of the first maneuver. For each patient, pulmonary function testing was to start at approximately the same time of the day between 7am and 10am, ±30 minutes from the time of testing at Visit 2. The pre-dose PFT was regarded as the trough FEV_1, and could be obtained within a 5-25 minute window prior to the morning dose of asthma and trial medications. The post-dose PFT measurements were obtained within 5 minutes of the 30- and 60-minute measurements and within 10 minutes of the 2- and 3-hour measurements, respectively. The highest FEV_1 within the 3-hour post-dosing interval was regarded as the peak FEV_1 response. In a subset of patients, 24hr PFTs were carried out after 24 weeks of treatment (Visit 6) at the following time points: 10 minutes pre-dose, and then 30 min, 60 min, 2 hr, 3 hr, 4 hr, 6 hr, 8 hr, 10 hr, 12 hr, 14 hr, 22 hr, 23 hr, and 24 hr post-dose.

Medication Restrictions for Pulmonary Function Testing (including Visit 1)

- At least 24-hour washout of long-acting (QDay) theophylline preparations

- At least 12-hour washout of short-acting (BID or more frequent) theophylline preparations, LABA, and LABA/ICS
- At least 8-hour washout of SABA and short-acting anticholinergic bronchodilators
- Daily dose of asthma and trial medication should be taken after the pre-dose PFT on clinic visits

Asthma Symptoms and Exacerbations

Patients documented worsening of asthma symptoms during the screening and treatment periods in the electronic diary of the AM3 and measured PEF twice daily. In addition, patient diary cards were used to document specific asthma symptoms, required medical treatment such as a change in asthma medication or need for medical care, or lost working days due to asthma worsening. Relevant information from the patient diary card was recorded in the eCRF. The investigators were instructed to report any deterioration of asthma as an AE regardless if the Sponsor's definition of asthma exacerbation was fulfilled or not.

The Applicant defined an asthma exacerbation as the following:

- an episode of progressive increase in one or more asthma symptoms (e.g., shortness of breath, cough, wheezing, and/or chest tightness) lasting for at least two consecutive days

  AND/OR

- a decrease of patient's best morning PEF of ≥30% from the patient's mean morning screening PEF for at least two consecutive days. Screening PEF was the mean value of all best morning PEF values obtained during the complete screening period including the morning of Visit 2.

An exacerbation was considered severe if it required treatment with systemic (including oral) corticosteroids (or doubling of pre-existing daily systemic corticosteroid dose) for at least 3 days. Courses of systemic corticosteroids that were separated by one week or more were treated as separate events. The onset was determined by the onset of first worsened symptom or first PEF deterioration. The end was determined by the investigator. Treatment of asthma exacerbations including initiation of systemic corticosteroids was left to the investigator's or treating physician's medical judgment. The recommended dose for oral glucocorticosteroids for the trial was 30 mg/day prednisolone or prednisolone equivalent for 7 days.

Reviewer Comment: An asymptomatic decrease in PEF, as described above, was considered an asthma exacerbation per protocol, regardless of being accompanied by asthma symptoms, need for additional asthma medication, or if considered medically relevant or not. I disagree that an asymptomatic decrease in PEF with no corresponding change in treatment constitutes a clinically meaningful asthma exacerbation, and as such, this issue will be addressed in the review of efficacy, Section 6.

Asthma Control Questionnaire

The Asthma Control Questionnaire (ACQ) was administered at screening (Visit 1) as part of the entry criteria and then at every visit from Visits 2-9. The questionnaire, as shown in Figure 7, includes seven questions, the first six completed by the patient and the last one by the clinic staff. Each question has a 7-point scale, and all questions are weighted equally. The score is the mean of the responses to all seven questions, and thus, the maximum score is 6 which indicates the lowest degree of asthma control.

Electronic peakflow meter with electronic diary

Patients received an Asthma Monitor® AM3 device at Visit 1 for use twice daily to record asthma symptom and quality of life questions, use of rescue medication, use of trial medication, and to measure PEFs and FEV1. Patients were instructed to perform peak expiratory flow maneuvers at approximately the same time of day (±30 minutes) between 7am and 10am and between 7pm and 10pm prior to administration of usual asthma therapy. All acceptable PEF and FEV1 values were stored in the AM3 with the date and time of reading, but the highest value of a triplicate maneuver was used for evaluation. The data from the AM3 device was downloaded at each visit and reviewed by the investigator with the patient.

Asthma Quality of Life Questionnaire (AQLQ(S))

The standardized Asthma Quality of Life Questionnaire was administered at clinic visits 2 to 6. The AQLQ(S), as shown in Figure 8, has 32 questions pertaining to the two weeks prior to the visit. Eleven questions refer to activity limitations, twelve questions refer to symptoms, five questions to emotional function, and another four questions to environmental stimuli. Each question has a 7-point scale.

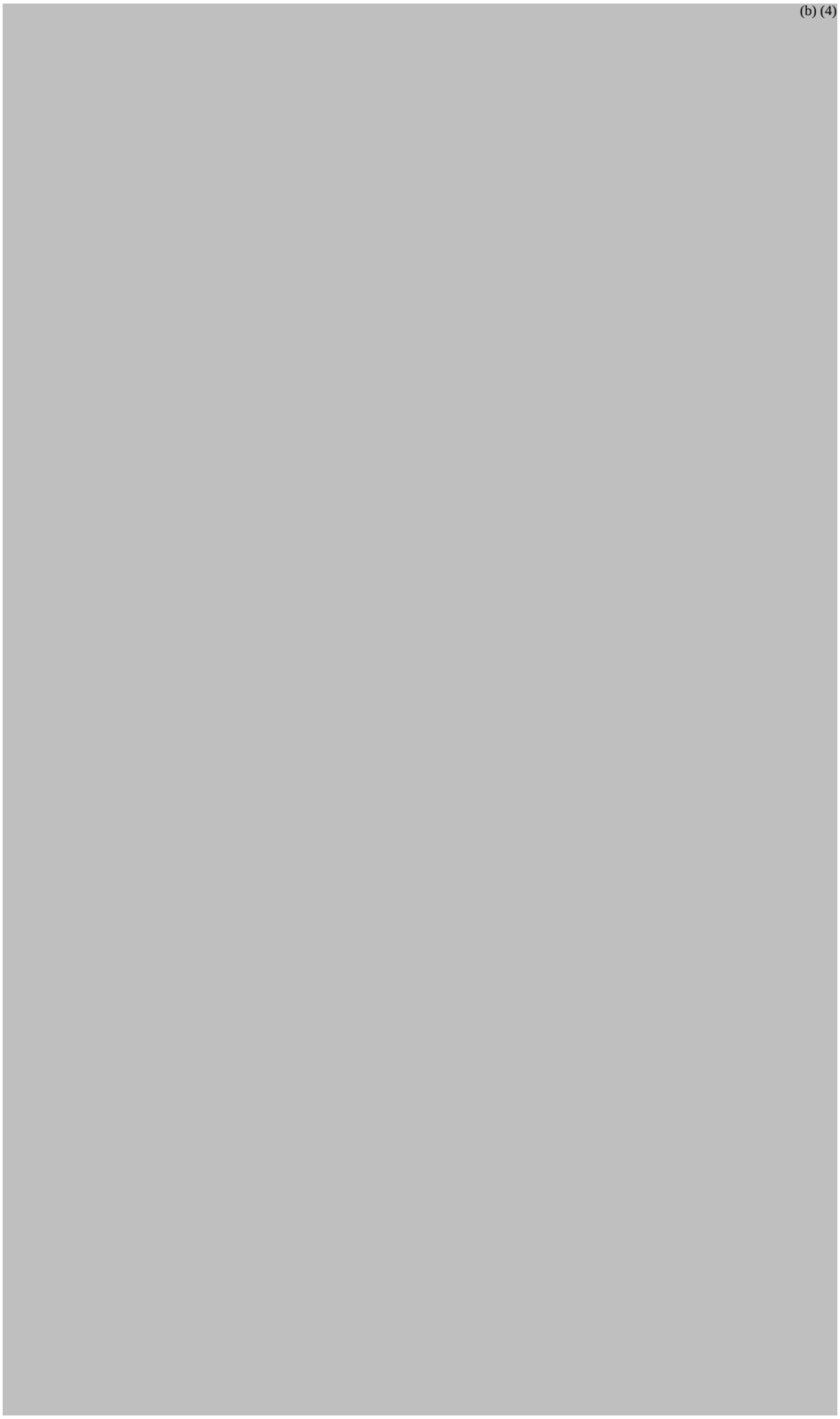

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Figure 8. Asthma Quality of Life Questionnaire (AQLQ)

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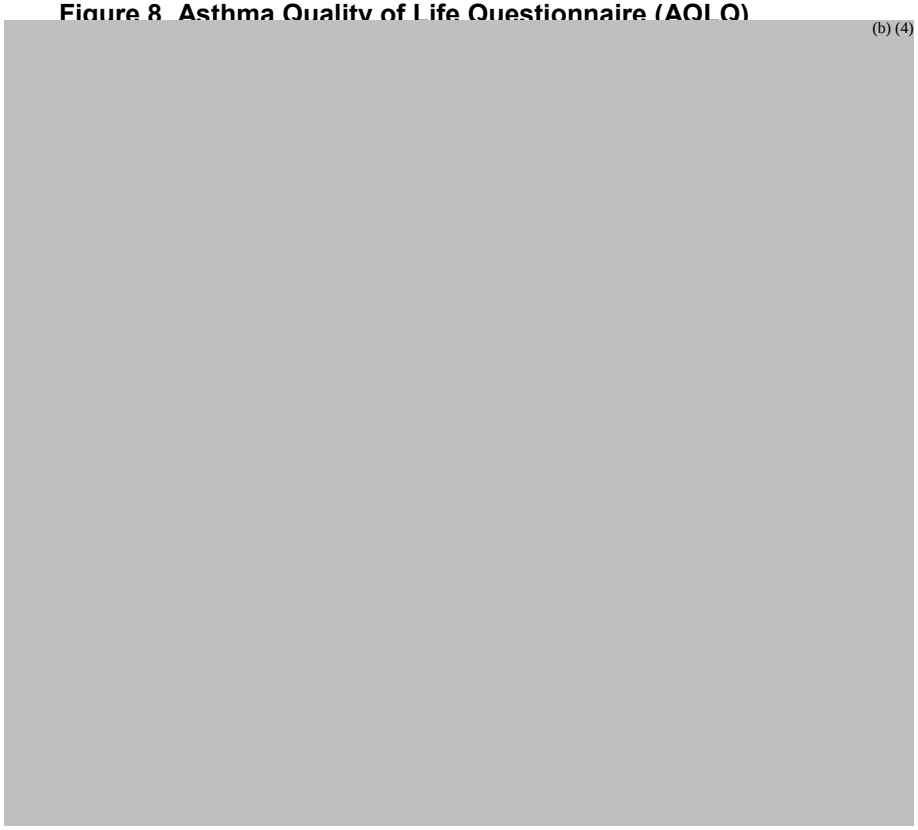

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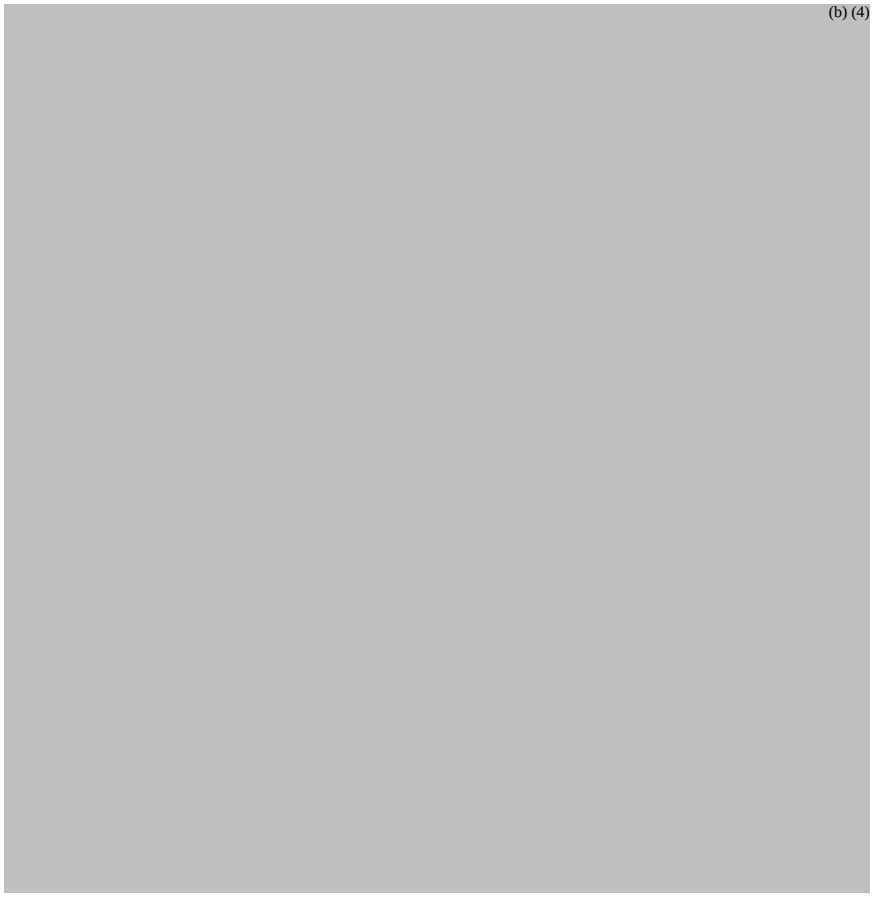

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Efficacy Endpoints

The two co-primary efficacy variables of the individual trials were peak FEV_1 within 3 hours post-dosing and trough FEV_1, both determined after a treatment period of 24 weeks. Peak FEV_1 response was defined as the change from baseline in peak FEV_1. Trough FEV_1 was defined as the FEV_1 measured at the -10 minute time point at the end of the dosing interval (24 hours post drug administration). Trough FEV_1 response was defined as the change from baseline in trough FEV_1. Baseline was the pre-treatment FEV_1 measured at Visit 2 in the morning 10 minutes prior to the morning dose of patient's usual asthma medication and first dose of trial medication.

An additional co-primary endpoint for the pooled analysis of data from trials 416 and 417 was the time to first severe asthma exacerbation after 48 weeks. The two trials were combined for analyses of asthma exacerbations to obtain adequate numbers of patients.

Secondary efficacy endpoints included:

- Peak (within 3 hours post dosing) and trough Forced Vital Capacity (FVC) at the end of the 24-week treatment period
- FEV (AUC_{0-3}) and FVC (AUC_{0-3}) at the of the 24-week treatment period. The AUC_{0-3} was calculated as area under the curve from 0 to 3 hours using the trapezoidal rule divided by the observation time (3 hours) reported in liters. Trough values were assigned to time 0.
- Individual FEV1 and FVC measurements at all time-points including peak, trough, and AUC_{0-3} during the 48-week treatment period.
- PEF a.m./p.m.: mean pre-dose morning and evening peak expiratory flow measured by patients at home
- FEV1 a.m./p.m.: mean pre-dose morning and evening peak expiratory flow measured by patients at home
- Number of asthma exacerbations per patient based on severity of the asthma exacerbation
- Number of patients with at least one asthma exacerbation based on severity during the 48-week treatment period
- Time to first hospitalization for asthma exacerbation during the 48-week treatment period
- Number of hospitalizations for asthma exacerbations per patient during the 48-week treatment period
- Number of patients with at least one hospitalization for asthma exacerbation during the 48-week treatment period
- Quality of Life as assessed by standardized Asthma Quality of Life Questionnaire (AQLQ) at all time-points during the 48-week treatment period
- Control of asthma assessed by the Asthma Control Questionnaire (ACQ) at all time-points during the 48-week treatment period

- Asthma symptoms as assessed by the patient's electronic diary during the 48-week treatment period
- Asthma symptom free days during the 48-week treatment period, defined as days with no reported symptoms and no use of rescue medication
- Use of PRN salbutamol (albuterol) rescue medication during the 48-week treatment period: number of puffs used per 24 hour period

Statistical Plan

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. The first two primary endpoints, change from baseline in FEV_1 $peak_{(0-3)}$ 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 data from trials 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 SR 5 µg over placebo was established for FEV_1 $peak_{(0-3)}$ at the 2.5% level (one-sided), then the treatment groups were compared for change in baseline in trough FEV_1. If superiority of SR 5 µg 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 in the pooled trials at the 5% level (two-sided).

The protocol pre-specified an interim analysis to re-adjust the sample size based on the observed hazard ratio on severe asthma exacerbations at the interim analysis. The interim analysis was performed once the total number of patients with at least one severe asthma exacerbation in the two trials reached 65. This analysis was conducted by an 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. In addition, the p-value was adjusted for the analysis of FEV1 endpoints with the increased sample size since the increase was based on the exacerbation endpoint.

Missing FEV_1 data was replaced with the least favorable FEV_1 value if a patient withdrew due to worsening of asthma. Missing baseline data was imputed. Data obtained after the intake of rescue medication was considered missing. Missing data

that had non-missing values from visits both before and after or had multiple consecutive missing values were linearly interpolated; baseline value was used if necessary. The last observation carried forward (LOCF) was used if there were no subsequent non-missing values for the missing visit.

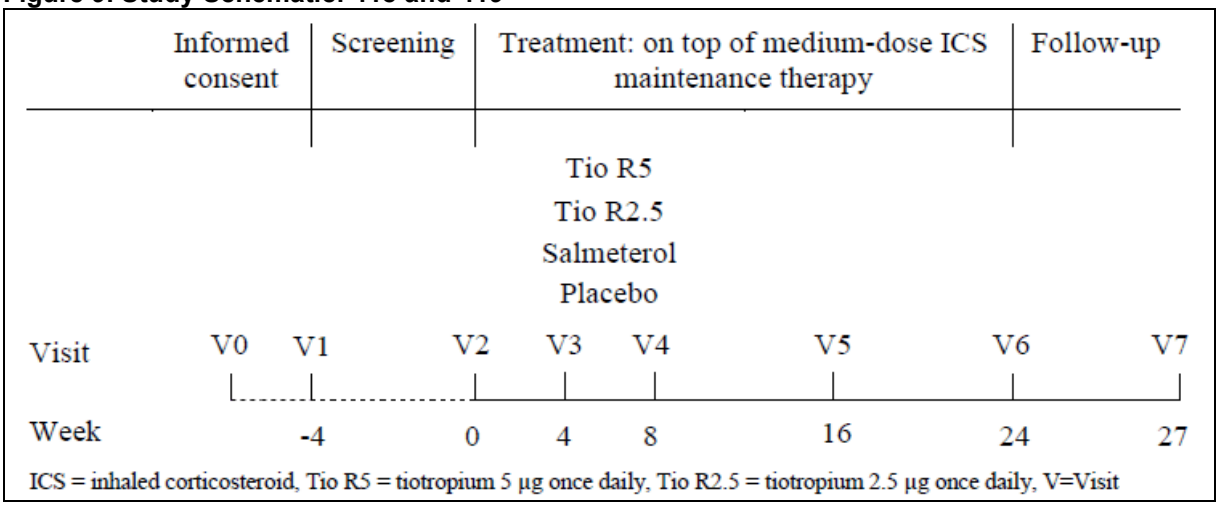
Safety
Safety assessments included adverse events, vital signs (pulse rate and seated blood pressure in conjunction with spirometry for first 3 hours post-dosing at each visit), physical examination at Visit 1 and last study visit, clinical laboratory testing at screening (CBC, chemistry – LDH, GGT, AST, ALT, Ca, Ph, Cr, K, Na, Cl), pregnancy testing at screening, 12-lead ECG at screening, and vital status information of prematurely discontinued patients.

Trials 205.418 and 205.419

Title	A Phase III randomized, double-blind, placebo-controlled, parallel-group trial to evaluate efficacy and safety of tiotropium inhalation solution delivered via Respimat inhaler (2.5 and 5 µg once daily) compared with placebo and salmeterol HFA MDI (50 µg twice daily) over 24 weeks in patients with moderate persistent asthma
Trial #	**205.418**
Study dates	Study initiated: September 7, 2010 Study completed: November 13, 2012 Final study report: April 10, 2013 (revised 5/23/14)
Sites	114 clinical study sites in 11 countries (Latvia, Poland, Russia, Brazil, China, Guatemala, India, Japan, Mexico, Peru, and the United States)
Trial #	**205.419**
Study dates	Study initiated: August 24, 2010 Study completed: November 7, 2012 Final study report: April 8, 2013 (revised 5/22/14)
Sites	124 clinical study sties in 11 countries (Poland, Romania, Brazil, China, Colombia, Germany, India, Japan, Mexico, Peru, and the United States)

Study Design
The design of these studies was similar to that of Studies 416 and 417 (i.e., randomized, double-blind, placebo-controlled, parallel-group). Major differences included the addition of multiple treatment arms (a lower 2.5 µg dose of tiotropium and an active comparator, salmeterol HFA MDI, along with a double-dummy control), a shorter treatment duration of 24 weeks, and a different patient population consisting of moderate persistent asthmatics.

Figure 9. Study Schematic: 418 and 419



Source: Module 5.3.5.1, Study 205.418 and 205.419 Protocols, Figure 9.1:1, p52

Patient Population

The target enrollment in Studies 418 and 419 was larger with approximately 1000 patients to be randomized into each trial. Patients in these trials had moderate persistent asthma that remained symptomatic despite background treatment with medium dose inhaled corticosteroids.

Entry criteria were similar to those of Studies 416 and 417 with differences noted below:
Inclusion Criteria

1. Minimum 3 month history of asthma at the time of enrollment
2. Bronchodilator reversibility at screening Visit 1, defined as FEV_1 increase of ≥12% and ≥200 mL occurring 15-30 minutes after 400 µg salbutamol or albuterol
3. Maintenance treatment with a medium, stable dose of inhaled corticosteroids (Table 8) alone or in a fixed combination with a LABA or SABA for at least 4 weeks prior to Visit 1
4. Pre-bronchodilator FEV_1 ≥ 60% and ≤ 90% predicted normal at screening
5. Compliance with electronic diary of at least 80%

Exclusion criteria were the same except for restrictions regarding disallowed medications (see Table 9).

Table 8. Definition of Medium-dose Inhaled Corticosteroids

Drug	*Medium daily Dose (µg)*
Beclomethasone dipropionate	≥500 and ≤1000
Budesonide	≥400 and ≤800
Ciclesonide	≥160 and ≤320
Flunisolide	≥1000 and ≤2000
Fluticasone	≥250 and ≤500
Mometasone furoate	≥400 and ≤800
Triamcinolone acetonide	≥1000 and ≤2000

Source: Module 5.3.5.1, Study 205.418 and Study 205.419 Protocols, Appendix 10.4, Table 10.4:1

Treatments

Compared to 416 and 417, these trials included two additional treatment arms: a lower dose of tiotropium and the active comparator, salmeterol HFA MDI. The timing of trial drug administration was also changed from morning to evening in order "to consider nocturnal control of airway patency".

Patients were randomized equally to one of the following double-blind treatment arms:

- Tiotropium 2.5 µg – 2 actuations from placebo MDI every morning and 2 actuations from placebo MDI every evening followed by 2 actuations of tiotropium from the 1.25 µg Respimat inhaler
- Tiotropium 5 µg – 2 actuations from placebo MDI every morning and 2 actuations from placebo MDI every evening followed by 2 actuations of tiotropium from the 2.5 µg Respimat inhaler
- Salmeterol – 2 actuations of 25 µg salmeterol HFA MDI every morning and 2 actuations of 25 µg salmeterol HFA MDI every evening followed by 2 actuations from the placebo Respimat inhaler
- Placebo – 2 actuations from placebo MDI every morning and 2 actuations from placebo MDI every evening followed by 2 actuations from the placebo Respimat inhaler

Trial medication was to be administered twice daily between 6 a.m. and 8 a.m. and between 6 p.m. and 8 p.m. each within ±30 minutes of the time of administration at Visit 2. Patients were instructed to take their background asthma medication followed by trial medication from the MDI and then the Respimat inhaler. Missed doses that were not taken within 4 hours of the recommended time frame were to be skipped until the next scheduled dose.

Open-label salbutamol (albuterol) HFA MDI inhalation aerosol (100 µg per actuation) was provided as rescue medication for use as needed at any point during the trial.

Concomitant Medications

The following table provides an overview of the medications that were required, permitted, or restricted before and during the trials.

Table 9. Required, Permitted, and Restricted Medications: Studies 418 and 419

Drug Class	Prior to Study (Visit 1)	Study Period		
		Screening Period	Treatment Period	Follow-up Period
Corticosteroids				
Inhaled	Required: stable medium dose for at least 4 weeks	Required: stable medium dose	Required: stable medium dose	Required: stable medium dose
Intranasal	Permitted	Permitted	Permitted	Permitted
Systemic	Not permitted for at least 4 weeks	Not permitted[1]	Not permitted[1]	Permitted
Beta-adrenergics/beta-blockers				
Inhaled SABA	Permitted	Permitted as rescue medication[2]	Permitted as rescue medication[2]	Permitted as rescue medication
Inhaled LABA	Permitted	Not permitted from 24 hours prior to Visit 1	Salmeterol study medication only	Permitted
Oral and patch beta-adrenergics	Not permitted for at least 4 weeks	Not permitted	Not permitted	Permitted[3]
Beta blockers	Not permitted for at least 4 weeks[4]	Not permitted[4]	Not permitted[4]	Permitted[3]
Anticholinergics				
Inhaled or nasal short-acting anticholinergics	Permitted	Not permitted from 8 hours prior to Visit 1	Not permitted	Permitted
Long-acting anticholinergics	Not permitted for at least 4 weeks	Not permitted	Study medication only	Not permitted
Combination inhaler products				
ICS/LABA or ICS/SABA	Permitted	Not permitted[5]	Not permitted	Permitted
Anticholinergic/SABA	Permitted	Not permitted from 8 hours prior to Visit 1	Not permitted	Permitted
Miscellaneous drugs				
Cromone	Not permitted for at least 2 weeks	Not permitted	Not permitted	Permitted
Antihistamines	Permitted	Permitted	Permitted	Permitted
Methylxanthines/PDE4 inhibitors	Not permitted for at least 2 weeks	Not permitted[6]	Not permitted[6]	Permitted
Mucolytics	Permitted	Permitted	Permitted	Permitted
Leukotriene modifiers	Permitted[7]	Permitted	Permitted	Permitted
Anti-IgE	Not permitted for at least 6 months	Not permitted	Not permitted	Permitted
Unapproved asthma medications/other investigational drugs	Not permitted for at least 4 weeks	Not permitted	Not permitted	Not permitted

Abbreviations: ICS=inhaled corticosteroid, LABA=long ac ing beta agonist, SABA=short acting beta agonist, PDE4=phosphodiesterase 4
[1]Temporary addition for treatment of acute asthma exacerbation allowed
[2]Required washout 8 hours prior to clinic visits
[3]Only re-introduction of previous medication use allowed
[4]Topical ophthalmic cardio-selective beta blocker medications for treatment of non-narrow angle glaucoma allowed
[5]Patient should be switched to ICS monotherapy product without changing the steroid dose
[6]Temporary addition of theophylline for treatment of acute asthma exacerbations allowed
[7]Dose must be stable for 4 weeks prior to Visit 1 and throughout the trial

Source: Module 5.3.5.1, Study 205.418 Protocol, Table 4.2.2.1:1, p196

Efficacy Variables

Pulmonary Function Testing Procedures

Predicted normal FEV_1 values at Visit 1 were calculated according to the ECSC reference criteria as in 416 and 417. Testing procedures were similar to those in 416 and 417, but primarily occurred in the evening due to the timing of trial medication administration. Pulmonary function testing was performed at each clinic visit between 6 p.m. and 8 p.m. and within ±30 minutes of the start of tests on Visit 2. A subset of patients also had 24-hour PFTs carried out after 24 weeks of treatment (Visit 6) according to the same schedule as described for 416 and 417. An additional subset of patients had PFTs carried out 5 minutes and 15 minutes post-dose after 16 weeks of treatment (Visit 5) to explore onset of action.

Medication restrictions for pulmonary function testing at clinic visits (including Visit 1) were similar except that an extended washout period of 24 hours was required for LABA and ICS/LABA products prior to Visit 1.

Asthma Exacerbations

The definition of an asthma exacerbation was identical to that in Studies 416 and 417.

ACQ and AQLQ(S)

Both questionnaires were as described for Studies 416 and 417.

Efficacy Endpoints

As in trials 416 and 417, the co-primary endpoints were peak FEV_1 within 3 hours of dosing and trough FEV_1 with tiotropium compared to placebo after 24 weeks of treatment. Peak, trough, and baseline FEV_1 were defined in a similar manner as in trials 416/417. For the analysis of pooled data from 418 and 419, the primary endpoint was the (binary) ACQ responder rate at the end of the 24-week treatment period. Responders were defined as improving by at least 0.5 on the ACQ.

Secondary and other endpoints were similar to those assessed in 416/417, albeit over 24 rather than 48 weeks, with the addition of the following:

- ACQ responder rate at the end of the 24-week treatment period for each individual trial
- $FEV_1(AUC_{0\text{-}12h})$, FEV_1 $(AUC_{12\text{-}24h})$, $FEV(AUC_{0\text{-}24h})$, FVC $(AUC_{0\text{-}12h})$, FVC $(AUC_{12\text{-}24h})$, FEV $(AUC_{0\text{-}24h})$ in a subset of patients after 24 weeks of treatment. Calculations were according to the trapezoidal rule as described above.
- Individual FEV_1 and FVC measurements at 5 and 15 minutes post dose including peak and AUC0-3h in a subset of patients
- Time to first severe asthma exacerbation during the 24-week treatment period for pooled data
- Time to first asthma exacerbation during the 24-week treatment period for pooled data

- The ACQ value at each visit during the 24-week treatment period

Analyses of hospitalizations for asthma exacerbations were not included in the efficacy evaluation.

Statistical Plan
The statistical methods used for analysis of the co-primary endpoints were the same as those described for trials 416 and 417. However, the stepwise manner approach to protect the overall type I error was slightly different given the inclusion of two SR doses. If superiority of SR 5 µg over placebo was established for change in baseline FEV_1 $peak_{(0-3)}$ at the 2.5% level (one-sided), then the superiority of SR 5 µg over placebo was tested for change in baseline in trough FEV_1 at the 2.5% level of significance (one-sided). If superiority was established, then the superiority of SR 2.5 µg over placebo for FEV_1 $peak_{(0-3)}$ and trough FEV_1, respectively, were tested at the 2.5% level of significance (one-sided). Missing FEV1 data was handled as previously described for trials 416 and 417.

ACQ responder rate was analyzed using Fisher's Exact Test.

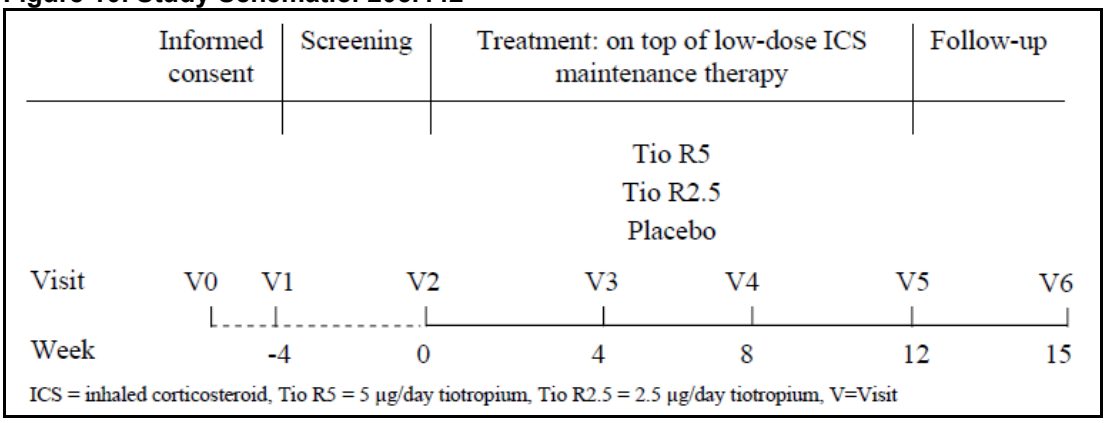
Safety
Safety assessments were the same as in trials 416 and 417.

Trial 205.442

Trial #	205.442
Title	A Phase III randomized, double-blind, placebo-controlled, parallel-group trial to evaluate efficacy and safety of tiotropium inhalation solution delivered via Respimat inhaler (2.5 and 5 µg once daily) compared to placebo over 12 weeks in mild persistent asthma
Study dates	Study initiated: April 7, 2011 Study completed: April 19, 2012 Final study report: January 9, 2013
Sites	65 clinical study sites in 12 countries (Argentina, Austria, Croatia, Estonia, Guatemala, Hungary, India, Italy, Korea, Latvia, Poland, and Slovakia)

Study Design
The design of trial 442 was similar to that of trials 416 and 417 (i.e., randomized, double-blind, placebo-controlled, parallel-group). Major differences included the addition of a lower 2.5 µg dose of tiotropium, a shorter treatment duration of 12 weeks, and a different patient population consisting of mild persistent asthmatics.

Figure 10. Study Schematic: 205.442



Source: Module 5.3.5.1, Study 205.442 CSR, Figure 9.1:1, p37

Patient Population

The target enrollment was 450 patients with mild persistent asthma who remained symptomatic despite treatment with low-dose inhaled corticosteroids.

Entry criteria were the same as for Studies 418 and 419 in moderate persistent asthma with differences noted below:

Inclusion Criteria

- Diagnosis of mild persistent asthma with symptoms despite current maintenance treatment with low doses of inhaled corticosteroids (Table 10) for at least 4 weeks prior to Visit 1

Exclusion Criteria

- Requiring > 10 puffs of rescue medication per 24 hours on 2 consecutive days during the screening period
- History of recent (6 months or less) of acute coronary syndrome (STEMI, Non-STEMI, unstable angina pectoris)
- Restrictions regarding disallowed medications (see Table 11)

Table 10. Definition of Low-dose Inhaled Corticosteroids

Drug	Low daily dose (µg)
Beclomethasone diproprionate	200 to 500
Budesonide	200 to 400
Ciclesonide	80 to 160
Flunisolide	500 to 1000
Fluticasone proprionate	100 to 250
Mometasone furoate	200 to 400
Triamcinolone acetonide	400 to 1000

Source: Module 5.3.5.1, Study 205.442 Protocol, Appendix 10.3, Table 10.3:1

Treatments

Patients were randomized equally to one of three treatment arms:

- Tiotropium 2.5 µg: 2 actuations of tiotropium 1.25 µg Respimat inhaler every evening
- Tiotropium 5 µg: 2 actuations of tiotropium 2.5 µg Respimat inhaler every evening
- Placebo: 2 actuations from the placebo Respimat inhaler every evening

Trial medication was to be administered once daily between 6 p.m. and 8 p.m. within ±30 minutes of the time of administration at Visit 2. Patients were instructed to take their background asthma medication followed by trial medication from the MDI and then the Respimat inhaler. Missed doses that were not taken within 4 hours of the recommended time frame were to be skipped until the next scheduled dose. As in the other studies, subjects were to withhold their evening dose of medications on clinic days which until after pre-dose procedures.

Open-label salbutamol (albuterol) HFA MDI inhalation aerosol (100 µg per actuation) was provided as rescue medication for use as needed at any point during the trial. Methods to monitor treatment compliance were the same as previously described for other trials.

Concomitant Medications

The following table provides an overview of the medications that were required, permitted, or restricted before and during the trial.

Table 11. Required, Permitted, and Restricted Medications: Trial 442

Drug Class	Prior to Study (Visit 1)	Study Period		
		Screening Period	Treatment Period	Follow-up Period
Corticosteroids				
Inhaled	Required: stable low dose for at least 4 weeks	Required: stable low dose	Required: stable low dose	Required: stable low dose
Topical	Permitted	Permitted	Permitted	Permitted
Systemic	Not permitted for at least 4 weeks	Not permitted[1]	Not permitted[1]	Permitted
Depot	Not permitted for at least 6 months	Not permitted	Note permitted	Note permitted
Beta-adrenergics/beta-blockers				
Inhaled SABA	Permitted	Permitted as rescue medication[2]	Permitted as rescue medication[2]	Permitted as rescue medication
Inhaled LABA	Not permitted for at least 4 weeks prior to Visit 0	Not permitted	Not permitted	Permitted
Oral beta-adrenergics	Not permitted for at least 4 weeks	Not permitted	Not permitted	Not permitted

Drug Class	Prior to Study (Visit 1)	Study Period		
		Screening Period	Treatment Period	Follow-up Period
Beta blockers	Not permitted for at least 4 weeks[3]	Not permitted[3]	Not permitted[3]	Not permitted[3]
Anticholinergics				
Inhaled or nasal short-acting anticholinergics	Permitted	Not permitted from 8 hours prior to Visit 1	Not permitted	Permitted
Long-acting anticholinergics	Not permitted for at least 4 weeks	Not permitted	Study medication only	Not permitted
Systemic (IV, IM, oral)	Not permitted for at least 2 weeks	Not permitted	Not permitted	Not permitted
Topical	Permitted	Permitted	Permitted	Permitted
Combination inhaler products				
ICS/LABA	Not permitted for at least 4 weeks prior to Visit 0	Not permitted	Not permitted	Permitted
ICS/SABA	Permitted	Not permitted[4]	Not permitted	Permitted
Anticholinergic/SABA	Permitted	Not permitted from 8 hours prior to Visit 1	Not permitted	Not permitted
Miscellaneous drugs				
Cromone	Not permitted for at least 2 weeks	Not permitted	Not permitted	Permitted
Antihistamines	Permitted	Permitted	Permitted	Permitted
Methylxanthines	Not permitted for at least 2 weeks	Not permitted[5]	Not permitted[5]	Permitted
Mucolytics	Permitted	Permitted	Permitted	Permitted
Leukotriene modifiers	Not permitted	Not permitted	Not permitted	Not permitted
Anti-IgE	Not permitted ever	Not permitted	Not permitted	Not permitted
Unapproved asthma medications/other investigational drugs	Not permitted for at least 4 weeks (or 6 half-lives)	Not permitted	Not permitted	Not permitted

Abbreviations: ICS=inhaled corticosteroid, LABA=long acting beta agonist, SABA=short acting beta agonist,
[1]Temporary addition for treatment of acute asthma exacerbation allowed
[2]Required washout 8 hours prior to clinic visits
[3]Topical ophthalmic cardio-selective beta blocker medications for treatment of non-narrow angle glaucoma allowed
[4]Patient should be switched to ICS monotherapy product without changing the steroid dose
[5]Temporary addition of theophylline for treatment of acute asthma exacerbations allowed
Source: Module 5.3.5.1, Study 205.442 Protocol, Table 4.2.2.1:1, p40

Efficacy Variables

Pulmonary function testing procedures including medication restrictions were the same as for Studies 418 and 419 with the following exceptions:

- No additional time points (e.g., 24-hour PFTs) were obtained
- Washout for LABAs was not relevant (disallowed medication)

Other efficacy assessments (ACQ, electronic peak flow meter, and asthma exacerbations) were the same as previously described.

Efficacy Endpoints
The primary efficacy endpoint was peak FEV_1 response within 3 hours post dosing determined at the end of the 12-week treatment period. The key secondary endpoint was the trough FEV_1 response at the end of the 12-week treatment period. Peak, trough, and baseline FEV_1 were defined as in other studies.

Secondary endpoints were measured at the 12-week time point and were the same as those described for other studies. No additional efficacy endpoints were assessed.

Statistical Plan
Efficacy analyses for the primary and key secondary endpoint were performed at 12 weeks according to the methods described for trials 418 and 419. However, because trough FEV_1 was a key secondary endpoint rather than co-primary endpoint, the stepwise manner to protect the overall type I error differed slightly. If the superiority of SR 5 µg over placebo was established for FEV_1 $peak_{0\text{-}3h}$, then the treatment groups were compared for change in baseline in FEV_1 $peak_{0\text{-}3h}$ for the superiority of SR 2.5 µg over placebo. Both tests were conducted at the 2.5% level of significance (one-sided). There was no multiplicity adjustment for the key secondary endpoint trough FEV_1. Missing data was handled in the same manner as in other trials.

Safety
Safety assessments were the same as previously described.

Trial 205.444

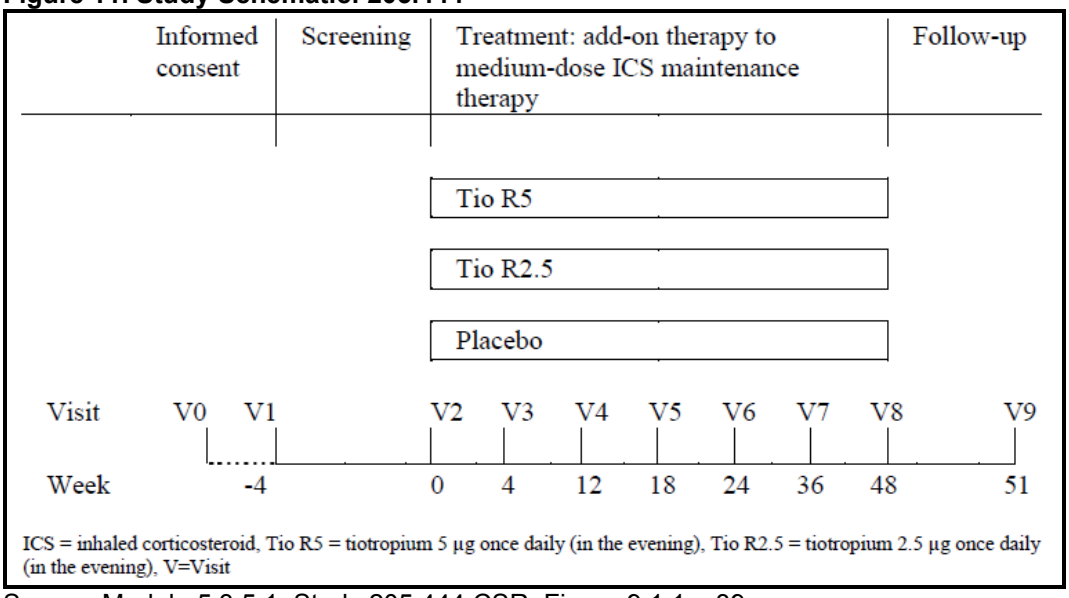
Trial #	205.444
Title	A phase III, randomized, double-blind, placebo-controlled, parallel group study to assess the efficacy and safety over 48 weeks of orally inhaled tiotropium bromide (2.5 µg and 5 µg once daily) delivered by the Respimat inhaler in adolescents (12 to 17 years old) with moderate persistent asthma.
Study dates	Study initiated: January 5, 2011 Study completed: December 27, 2013 Final study report: June 18, 2014
Sites	65 clinical study sites in 12 countries (Germany, Spain, Hungary, Italy, Slovakia, Latvia, Ukraine, Russia, Korea, Mexico, Chile, and the United States)

Objective
The primary objective of the trial was to demonstrate the superiority of tiotropium once daily in the evening with regard to primary pulmonary function endpoints after 24 weeks of treatment as compared to placebo.

Study Design
The design of trial 444 was similar to that of trials 416 and 417 (i.e., randomized, double-blind, placebo-controlled, parallel-group). Major differences included the addition of a lower 2.5 µg dose of tiotropium and evaluation of a different patient population consisting of adolescents with moderate persistent asthma. Although efficacy endpoints

were analyzed after 24 weeks of treatment (Visit 6), patients received blinded treatment for a total of 48 weeks.

Figure 11. Study Schematic: 205.444



Source: Module 5.3.5.1, Study 205.444 CSR, Figure 9.1:1, p39

Patient Population

Target enrollment was 381 adolescents between the ages of 12 and 17 years with moderate persistent asthma who remained symptomatic on background medication.

Entry criteria were similar to those described for trials 418 and 419 with differences noted below.

Inclusion Criteria

- Male or female between 12 and 17 years of age
- If patients in the lower age range (12-14 years) exhibited a very small total lung volume, positive reversibility could be based solely on the relative (≥12%) post-bronchodilator response
- Maintenance treatment with inhaled corticosteroids at a stable medium dose either as mono treatment or in combination with a LABA or leukotriene modifier for at least 4 weeks prior to Visit 1. For lower age groups (12-14 years), the dosing recommendations for “children > 5 years” could be applied (see Table 12). LABAs must be stopped at least 72 hours prior to Visit 1.

Exclusion Criteria

- History of congenital or acquired heart disease, and/or hospitalization for cardiac syncope or failure during past year
- Restrictions regarding concomitant medications (see Table 13)

Table 12. Definition of Medium-dose Inhaled Corticosteroid: Trial 444

Drug	Medium daily dose (µg)	
	Adults / adolescents	Children > 5 years
Beclomethasone diproprionate	≥ 500 - ≤ 1000	≥ 200 - ≤ 400
Budesonide	≥ 400 - ≤ 800	≥ 200 - ≤ 400
Ciclesonide	≥ 160 - ≤ 320	≥ 160 - ≤ 320
Flunisolide	≥ 1000 - ≤ 2000	≥ 750 - ≤ 1250
Fluticasone proprionate	≥ 200 - ≤ 500	≥ 200 - ≤ 500
Mometasone furoate	≥ 400 - ≤ 800	≥ 200 - ≤ 400
Triamcinolone acetonide	≥ 1000 - ≤ 2000	≥ 800 - ≤ 1200

Source: Module 5.3.5.1, Study 205.444 Protocol, Table 3.3.2:1, p141

Treatments

Trial and rescue medication was exactly as described for Study 444. Instructions for administration of medications were also the same except that the timing of doses was slightly earlier, between 5 p.m. and 7 p.m.

For treatment of asthma exacerbations, the recommended initial dose of systemic corticosteroids was 0.5 to 1 mg/kg/day of prednisolone or equivalent.

Concomitant Medications

The following table provides an overview of the medications that were required, permitted, or restricted before and during the trial.

Table 13. Required, Permitted, and Restricted Medications: Trial 444

Drug Class	Prior to Study (Visit 1)	Study Period		
		Screening Period	Treatment Period	Follow-up Period
Corticosteroids				
Inhaled	Required: stable medium dose for at least 4 weeks	Required: stable medium dose	Required: stable medium dose	Required: stable medium dose
Topical	Permitted	Permitted	Permitted	Permitted
Systemic	Not permitted for at least 4 weeks	Not permitted[1]	Not permitted[1]	Not permitted[1]
Beta-agonists and blockers				
Inhaled SABA	Permitted	Permitted as rescue medication[2]	Permitted as rescue medication[2]	Permitted as rescue medication
Inhaled LABA	Not permitted for at least 3-4 days	Not permitted	Not permitted	Permitted
Systemic beta-agonist	Not permitted	Not permitted[1]	Not permitted[1]	Not permitted[1]
Beta blockers	Not permitted[3]	Not permitted[3]	Not permitted[3]	Not permitted[3]
Anticholinergics				
Inhaled or nasal short-acting anticholinergics	Permitted[2]	Not permitted[1]	Not permitted[1]	Permitted
Long-acting anticholinergics	Not permitted for at least 4 weeks	Not permitted	Study medication only	Not permitted

Drug Class	Prior to Study (Visit 1)	Study Period		
		Screening Period	Treatment Period	Follow-up Period
Combination inhaler products				
ICS/LABA	Not permitted for at least 3 days[4]	Not permitted	Not permitted	Permitted
ICS/SABA	Permitted	Not permitted[2,4]	Not permitted	Permitted
Anticholinergic/SABA	Permitted	Not permitted[2]	Not permitted	Not permitted
Miscellaneous drugs				
Antihistamines	Permitted	Permitted	Permitted	Permitted
Anti-IgE	Not permitted for at least 6 months	Not permitted	Not permitted	Not permitted
Cromolyn sodium or nedocromil sodium	Permitted[5]	Permitted	Permitted	Permitted
Leukotriene modifiers	Permitted[5]	Permitted	Permitted	Permitted
Methylxanthines	Not permitted for at least 2 weeks	Not permitted[6]	Not permitted[6]	Not permitted
Mucolytics	Permitted	Permitted	Permitted	Permitted
Unapproved asthma medications/other investigational drugs	Not permitted for at least 4 weeks (or 6 half-lives)	Not permitted	Not permitted	Not permitted

Abbreviations: ICS=inhaled corticosteroid, LABA=long acting beta agonist, SABA=short acting beta agonist,
[1]Temporary addition for treatment of acute asthma exacerbation allowed
[2]Required washout 8 hours prior to clinic visits
[3]Topical ophthalmic cardio-selective beta blocker medications for treatment of non-narrow angle glaucoma allowed
[4]Patient should be switched to ICS monotherapy product without changing the steroid dose
[5]If dose is stable for at least 4 weeks prior to trial and remains stable throughout trial
[6]Temporary addition of short acting theophylline for treatment of acute asthma exacerbations allowed
Source: Module 5.3.5.1, Study 205.444 Protocol, Table 4.2.2.1:1, p34

Efficacy Variables

Pulmonary function testing procedures including medication restrictions were similar to those described for trials 418 and 419 with the following exceptions:

- Predicted equations for FEV1, FVC, and FEF_{25-75} derived from Wang et al[5]
- Pulmonary function testing started between 5 p.m. and 7 p.m.
- No additional time points (e.g., 24-hour PFTs) were obtained
- 72-hour washout for LABAs and ICS/LABAs prior to Visit 1
- 24-hour washout for leukotriene modifiers

Other efficacy assessments (ACQ, electronic peak flow meter, and asthma exacerbations) were the same as previously described.

[5] Wang X, Dockery DW, Wypij D, Gold DR, Speizer FE, Ware JH, Ferris BG. Pulmonary function growth velocity in children 6 to 18 years of age. *Am Rev Respir Dis.* 1993; 148: 1502-1508

Efficacy Endpoints
The primary endpoint was peak FEV1 response within 3 hours post-dosing determined at the end of 24 weeks of treatment. The key secondary endpoint was trough FEV1 at 24 weeks. Peak, trough, and baseline FEV1 were defined in the same manner as in other trials.

Secondary endpoints were measured at the 24-week time point and were the same as those described for other studies. One additional endpoint included the mean forced expiratory flow between 25% and 75% of the FVC or maximum midexpiratory flow (FEF_{25-75}).

Statistical Plan
Efficacy analyses were performed at 24 weeks as described for trial 442.

Safety
Safety assessments were the same as previously described.

Trial 205.456

Trial #	205.456
Title	A randomized, double-blind, placebo-controlled, parallel-group trial to evaluate efficacy and safety of tiotropium inhalation solution delivered via Respimat inhaler (2.5 µg and 5 µg once daily) over 12 weeks as add-on controller therapy on top of usual care in adolescents (12 to 17 years old) with severe persistent asthma
Study dates	Study initiated: January 31, 2011 Study completed: October 16, 2013 Final study report: April 8, 2014
Sites	68 clinical study sites in 14 countries (Argentina, Australia, Bulgaria, Germany, Guatemala, Hungary, Israel, Italy, Latvia, Mexico, Norway, Philippines, Portugal, South Africa, Ukraine, the United States)

Study Design
The design was identical to the other trial in adolescents, trial 444, with the two major differences: a shorter treatment duration of 12 weeks and a more severe asthma population.

Patient Population
A total of 375 adolescents (125 per group) with severe persistent asthma were to be randomized into the trial. The protocol was amended to increase the sample size from a total of 125 based on a revision of the expected standard deviation for the primary endpoint.

Entry criteria were the same as for adolescent trial 444 with the following exceptions:
Inclusion Criteria

- Maintenance treatment with a high dose inhaled corticosteroid in combination with another controller medication (e.g., LABA or leukotriene modifier) OR a

medium dose inhaled corticosteroid in combination with two other controller medications (e.g., LABA and/or leukotriene modifier and/or a sustained released theophylline) for at least 4 weeks before Visit 1. Refer to Table 6 and Table 8 for definitions of high and medium dose ICS for older adolescents. For the lower age group (12-14 years old), the inhaled corticosteroid dosing recommendations for children >5 years may have been used if appropriate (Table 14).

Exclusion Criteria

- Restricted medication usage (see Table 15)

Table 14. Definition of Medium and High-dose ICS for children >5 years old

Drug	Medium daily dose (µg)	High daily dose (µg)
Beclomethasone dipropionate	≥200 – 400	>400
Budesonide	≥200 – 400	>400
Budesonide-Neb	≥500 – 1000	>1000
Ciclesonide	≥160 – 320	>320
Flunisolide	≥750 – 1250	>1250
Fluticasone propionate	≥200 – 500	>500
Mometasone furoate	≥200 – 400	>400
Triamcinolone acetonide	≥800 - 1200	>1200

Source: Module 5.3.5.1, Study 202.456, Protocol, Table 10.3:2, p232

Treatments

Trial and rescue medications and dosage administration were identical to those in trial 444; however, concomitant and disallowed medications differed and are listed in the table below.

Table 15. Required, Permitted, and Restricted Medications: Trial 456

Drug Class	Prior to Study (Visit 1)	Study Period		
		Screening Period	Treatment Period	Follow-up Period
Corticosteroids				
Inhaled	Required: stable medium-high dose for at least 4 weeks	Required: stable medium to high dose	Required: stable medium to high dose	Required: stable medium to high dose
Topical	Permitted	Permitted	Permitted	Permitted
Systemic	Permitted[1]	Permitted[1]	Permitted[1]	Permitted[1]
Beta-agonists and blockers				
Inhaled SABA	Permitted	Permitted as rescue medication[2]	Permitted as rescue medication[2]	Permitted as rescue medication
Inhaled LABA	Permitted[3]	Permitted[3]	Permitted[3]	Permitted
Systemic beta-agonists	Not permitted for	Not permitted[1]	Not permitted[1]	Not permitted[1]

Drug Class	Prior to Study (Visit 1)	Study Period		
		Screening Period	Treatment Period	Follow-up Period
	at least 4 weeks			
Beta blockers	Not permitted for at least 4 weeks[4]	Not permitted[4]	Not permitted[4]	Not permitted[4]
Anticholinergics				
Inhaled or nasal short-acting anticholinergics	Permitted	Not permitted[1,2]	Not permitted[1]	Permitted
Long-acting anticholinergics	Not permitted for at least 4 weeks	Not permitted	Study medication only	Not permitted
Systemic (IV, IM, oral, SC)	Not permitted for at least 4 weeks	Not permitted	Not permitted	Not permitted
Combination inhaler products				
ICS/LABA	Permitted	Permitted[3]	Permitted[3]	Permitted
ICS/SABA	Permitted	Not permitted[2,5]	Not permitted	Permitted
Anticholinergic/SABA	Permitted	Not permitted[2]	Not permitted	Permitted
Miscellaneous drugs				
Anti-IgE	Permitted[6]	Permitted	Permitted	Permitted
Antihistamines	Permitted	Permitted	Permitted	Permitted
Cromones	Permitted[7]	Permitted	Permitted	Permitted
Leukotriene modifiers	Permitted[7]	Permitted[8]	Permitted[8]	Permitted
Methylxanthines	Permitted[9]	Permitted[3,8]	Permitted[3,8]	Permitted
Mucolytics	Permitted	Permitted	Permitted	Permitted
Unapproved asthma medications/other investigational drugs	Not permitted for at least 4 weeks (or 6 half-lives)	Not permitted	Not permitted	Not permitted

Abbreviations: ICS=inhaled corticosteroid, LABA=long acting beta agonist, SABA=short acting beta agonist,
[1]Prednisolone ≤ 5 mg/day or ≤ 10 mg every other day (or prednisolone equivalent)
[2]Required washout 8 hours prior to clinic visit PFTs
[3]Required washout 12 hours prior to clinic visit PFTs
[4]Topical ophthalmic cardio-selective beta blocker medications for treatment of non-narrow angle glaucoma allowed
[5]Patient should be switched to ICS monotherapy product without changing the steroid dose
[6]Dose must be stable for 6 months prior to Visit 1 and throughout the trial
[7]Dose must be stable for at least 4 weeks prior to Visit 1 and throughout trial
[8]Required washout 24 hours prior to clinic visit PFTs
[9]For long-acting preparations, dose must be stable for 2 weeks prior to Visit 1 and throughout the trial
Source: Module 5.3.5.1, Study 205.456 Protocol, Table 4.2.2.1:1, p52

Efficacy Variables

Pulmonary function testing procedures including medication restrictions were similar to those described for trial 444 with the following exceptions:

- Pulmonary function testing started between 4:35 p.m. and 6:55 p.m. at Visit 2
- 12-hour washout for LABAs and ICS/LABAs
- 12-hour washout of short-acting methylxanthines
- 24-hour washout of long-acting methylxanthines

Other efficacy assessments (ACQ, electronic peak flow meter, and asthma exacerbations) were the same as previously described.

Efficacy Endpoints
The primary endpoint was peak FEV1 response within 3 hours post-dosing determined at the end of the 12-week treatment period. The key secondary endpoint was trough FEV1 at 12 weeks. Peak, trough, and baseline FEV1 were defined in the same manner as in other trials.

Secondary endpoints were measured at the 12-week time point and were the same as those described for trial 444.

Statistical Plan
Efficacy analyses were performed at 12 weeks as described for trial 442.

Safety
Safety assessments were the same as previously described.

The following table highlights the key differences among phase 3 trials in terms of patient populations, background medications, and design.

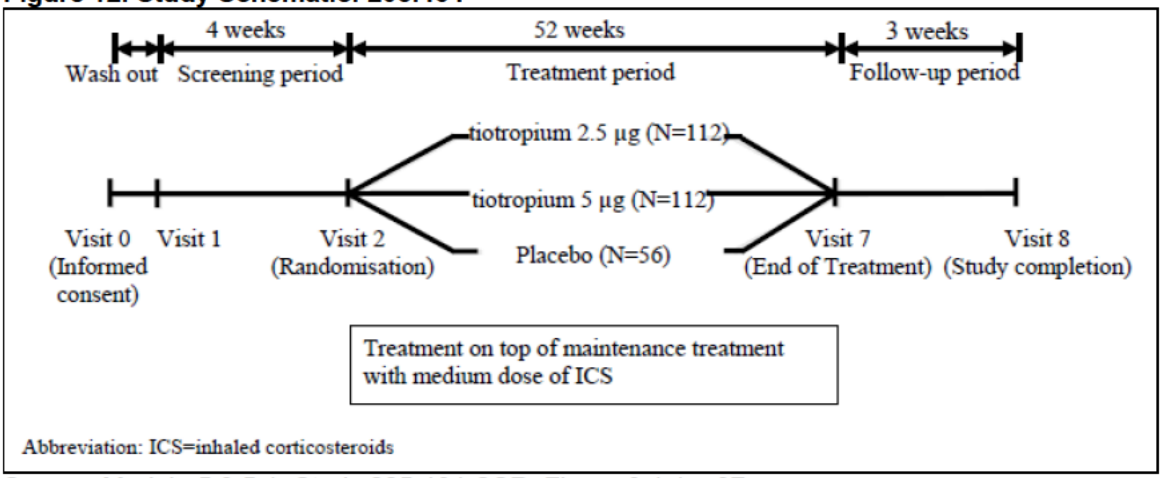
Trial 205.464

Trial #	205.464
Title	A Phase III randomized, double-blind, placebo-controlled, parallel-group trial to evaluate safety and efficacy of tiotropium inhalation solution delivered via Respimat inhaler (2.5 and 5 µg once daily) compared with placebo over 52 weeks in patients with moderate to severe persistent asthma
Study dates	Study initiated: April 12, 2011 Study completed: April 23, 2013 Final study report: September 19, 2013
Sites	54 clinical study sites in Japan

Objectives
The primary objective of this trial was to evaluate the long-term safety of tiotropium compared with placebo on top of maintenance therapy with inhaled corticosteroids with evaluation of long-term efficacy a secondary objective.

Study Design
The design was similar to that of the other phase 3 trials (i.e., randomized, double-blind, placebo-controlled, and parallel-group) with the following differences: a randomization scheme of 2:2:1, a 52-week treatment period, and a patient population with moderate to severe persistent asthma.

Figure 12. Study Schematic: 205.464



Source: Module 5.3.5.1, Study 205.464 CSR. Figure 9.1:1, p37

Patient Population

Target enrollment was 280 randomized patients with moderate to severe asthma.

Key inclusion and exclusion criteria were the same as for Studies 418 and 419 with minor differences in restrictions regarding concomitant medications, the most notable being the permission to use LABAs during the treatment period. See Table 16 for details regarding concomitant medication usage.

Treatments and Concomitant Medications

Patients were randomized 2:2:1 to one of three treatment groups: SR 2.5 µg daily, SR 5 µg daily, or placebo. Medications and instructions for administration were similar to those described for Studies 418 and 419.

Table 16. Required, Permitted, and Restricted Medications: Trial 464

Drug Class	Prior to Study (Visit 1)	Study Period		
		Screening Period	Treatment Period	Follow-up Period
Corticosteroids				
Inhaled	Required: stable medium dose for at least 4 weeks	Required: stable medium dose[1]	Required: stable medium dose[1]	Required: stable medium dose
Systemic	Not permitted for at least 4 weeks	Not permitted[1]	Not permitted[1]	Permitted
Beta-agonists and blockers				
Inhaled SABA	Permitted	Permitted as rescue medication[2]	Permitted as rescue medication[2]	Permitted as rescue medication
Inhaled and patch LABAs	Permitted[3]	Permitted[4]	Permitted[4]	Permitted
Oral beta-agonists	Not permitted for at least 4 weeks	Not permitted	Not permitted	Permitted[5]

Drug Class	Prior to Study (Visit 1)	Study Period		
		Screening Period	Treatment Period	Follow-up Period
Beta blockers	Not permitted for at least 4 weeks[6]	Not permitted[b]	Not permitted[b]	Permitted[5]
Anticholinergics				
Inhaled or nasal short-acting anticholinergics	Permitted	Not permitted from 8 hours prior to Visit 1	Not permitted	Permitted
Long-acting anticholinergics	Not permitted for at least 4 weeks	Not permitted	Study medication only	Not permitted
Combination inhaler products				
ICS/LABA	Permitted[3,7]	Permitted[4]	Permitted[4]	Permitted
Miscellaneous drugs				
Cromone	Permitted[3]	Permitted	Permitted	Permitted
Antihistamines	Permitted[3]	Permitted	Permitted	Permitted
Methylxanthines	Permitted[3]	Permitted[8]	Permitted[8]	Permitted
Mucolytics	Permitted[3]	Permitted	Permitted	Permitted
Leukotriene modifiers	Permitted[3]	Permitted	Permitted	Permitted
Anti-IgE	Not permitted for at least 6 months	Not permitted	Not permitted	Permitted
Unapproved asthma medications/other investigational drugs	Not permitted for at least 4 weeks	Not permitted	Not permitted	Not permitted

Abbreviations: ICS=inhaled corticosteroid, LABA=long acting beta agonist, SABA=short acting beta agonist
[1]Temporary addition for treatment of acute asthma exacerbation allowed
[2]Required washout 8 hours prior to PFTs
[3]Dose must be stable at least 4 weeks prior to Visit 1 and throughout the trial
[4]Required washout 24 hours prior to PFTs
[5]Only re-introduction of previous medication use allowed
[6]Topical ophthalmic cardio-selective beta blocker medications for treatment of non-narrow angle glaucoma allowed
[7]Patient should be switched to ICS monotherapy product without changing the steroid dose 24 hours prior to PFTs
[8]Temporary addition of theophylline for treatment of acute asthma exacerbations allowed
Source: Module 5.3.5.1, Study 205.464 Protocol, Table 4.2.2.1:1, p126

Efficacy

Assessments for efficacy included pulmonary function testing, asthma exacerbations, the ACQ, and electronic peak flow meter with diary (AM3) as described for other studies. Medication washout periods prior to PFTs were the same as in Studies 418 and 419. No primary efficacy endpoints were defined since the primary purpose of this trial was to evaluate the long-term safety of tiotropium delivered via the Respimat inhaler.

Safety

Safety assessments included adverse events, physical examination, pulse rate and blood pressure at all visits, clinical labs (hematology, chemistry) at screening and follow-up, 12-lead ECG at screening and follow-up, and vital status information for all randomized patients.

6 Review of Efficacy

Efficacy Summary

The primary clinical data to support the efficacy of Spiriva Respimat (SR) for the proposed indication of add-on maintenance treatment of asthma in patients 12 years of age and older who remain symptomatic on ICS, consisted of a total of seven trials: five in adults and two in adolescents. These consisted of replicate 48-week trials in severe asthma (416/417), replicate 24-week trials in moderate asthma (418/419), and a 12-week trial in mild asthma (442) as well as a 12-week trial in adolescents with severe asthma (456) and 48-week trial in adolescents with moderate asthma (444). The co-primary or primary and key secondary endpoints in all trials were peak FEV_1 measured within 3 hours post-dose (FEV_1 $peak_{(0-3)}$) and trough FEV_1. As additional efficacy support, all trials captured asthma exacerbations as a secondary endpoint with time to first "severe" exacerbation being a primary endpoint for the pooled analysis of the 48-week replicate trials (416 and 417).

Notably, subjects in trials 416 and 417 differed from typical asthma patients and the other clinical trial subjects in that they were all required to have fixed obstruction with relatively minimal post-bronchodilator reversibility. Additionally, compared to the other adult trials, these subjects were older with a higher incidence of past tobacco use, and virtually all were on background LABA therapy prior to entering the trial. Thus, by nature of the entry criteria, the trial populations in 416 and 417 likely included subjects who may have had COPD or Asthma-COPD overlap syndrome. This fact was also noted in an editorial response to the publication of these trials in the New England Journal of Medicine[6,7]. While total serum IgE levels and peripheral blood eosinophil counts suggest the presence of some degree of atopy in the 416 and 417 trial populations, whether or not this can be extrapolated to the presence of allergic asthma is questionable.

In six of the seven trials, SR 5 µg once-daily demonstrated modest, but statistically significant, improvements in FEV_1 $peak_{(0-3)}$ and trough response. The difference from placebo at the time of the primary endpoint analysis for trials 416, 417, 418, 419, 442, 444, and 456 were 0.086, 0.154, 0.198, 0.169, 0.128, 0.174, and 0.090 L, respectively, for FEV_1 $peak_{(0-3)}$ and 0.088, 0.111, 0.152, 0.133, 0.122, 0.117, 0.054 L, respectively, for trough FEV1. In the five trials that included an SR 2.5 µg once-daily treatment arm (trials 418, 419, 442, 444, and 456), the 2.5 µg dose also demonstrated statistically significant responses in FEV_1 $peak_{(0-3)}$ and trough compared to placebo; moreover, the mean treatment difference was numerically better with SR 2.5 than SR 5 in four of the

[6] Kerstjens HA, et al. Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med.* 2012 Sep 27; 367 (13): 1198-207
[7] Bel EH. Tiotropium for asthma – promise and caution. *N Engl J Med.* 2012 Sep 27; 367 (13): 1257-9

five trials. The difference from placebo at the time of the primary endpoint analysis for these trials in the above-mentioned order were 0.236, 0.211, 0.159, 0.134, and 0.111 L for FEV_1 $peak_{(0-3)}$ and 0.185, 0.176, 0.110, 0.084, and 0.115 L for trough FEV_1. As evident from the phase 3 asthma trials, it is notable that there was little to no added bronchodilator benefit for the 5 µg dose over the 2.5 µg dose. In fact, in four of five trials where the two doses were compared, the higher 5 µg dose response was consistently lower.

Unlike β2-agonists which have long-been established as bronchodilators in asthma, a similar beneficial role for anticholinergics in asthma has not yet been clearly demonstrated. Due to the modest benefit of SR on FEV_1, an evaluation of the asthma exacerbations in this program was important to establishing a clinically meaningful benefit of SR for asthma. Because the analyses of exacerbations were derived from pooled data rather than replicate trials, a reduction in exacerbations serves to support SR as a bronchodilator in asthma, (b) (4) . Although all trials captured exacerbations as a secondary endpoint using the same definition, the frequency of exacerbation events in the 12-week trials was too low to draw any conclusions; therefore, only data from the 24 to 48-week trials are presented in this review.

Across trials, the Applicant defined any asthma exacerbation as a progressive increase in asthma symptoms or a decrease in PEF of ≥30% for at least two consecutive days. By this measure, an asymptomatic decrease in PEF was considered an asthma exacerbation per protocol regardless of being accompanied by asthma symptoms, need for additional asthma medication, or if considered medically relevant or not. “Severe” exacerbations were defined as the subset of exacerbations requiring initiation of treatment with systemic (including oral) corticosteroids or doubling of current oral corticosteroid dose for at least 3 days. Although the definition of a “severe” exacerbation is generally per consensus guidelines[8], the majority of these exacerbations were defined by use of oral corticosteroids, rather than what might be considered the more “severe” aspect of the definition, specifically inpatient hospitalizations or ED visits. As a result, for the purposes of this review and to avoid confusion with the regulatory term “serious”, events meeting the aforementioned definition of any asthma exacerbation are referred to as “asthma worsening”, and the subset of exacerbations categorized as “severe” by the Applicant are referred to as simply “asthma exacerbations”.

Trials 416 and 417 were each 48 weeks in duration and enriched with patients who had experienced one or more asthma exacerbations in the past year. Time to first asthma

[8] Reddel et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med*. 2009 Jul 1; 180 (1):59-99

exacerbation was the pre-specified primary endpoint for the pooled analysis. Once-daily treatment with SR 5 demonstrated a statistically significant improvement compared with placebo regarding time to first asthma exacerbation. In addition, fewer subjects experienced an asthma-related hospitalization in the SR 5 group compared to placebo. While trials 416 and 417 were the longest in duration and evaluated a clinically important event in difficult to control asthma, all subjects had fixed obstructive airway disease to the extent that would fulfill spirometric criteria for the diagnosis of COPD. Because SR 5 has already demonstrated efficacy for reducing exacerbations in COPD, the generalization of exacerbation data from these trials to broader asthma populations is problematic. In addition, neither of these trials evaluated SR 2.5 which consistently outperformed SR 5 with regard to FEV_1 treatment effects. For these reasons, exacerbation data captured as a secondary endpoint in trials of moderate asthmatics (418, 419, and 444) were evaluated as well.

In the pooled analysis of exacerbation data from trials 418 and 419, the risk of first asthma exacerbation was reduced in all active treatment arms compared to placebo with hazard ratios of 0.72, 0.50, and 0.75 for SR 5, SR 2.5, and salmeterol HFA groups, respectively. Although reported p-values are nominal, only SR 2.5 resulted in a statistically significant reduction in asthma exacerbations over placebo (95% CI 0.30, 0.84; p=0.008). In trial 444 in adolescents, hazard ratios for time to first asthma exacerbation again favored active treatment over placebo, more so with SR 5 than SR 2.5; however, neither reached statistical significance. These results suggest that there is no significant loss of efficacy between SR 5 and SR 2.5 with regard to reduction in asthma exacerbations.

In sum, per my review of the efficacy data, SR 2.5 µg once daily appears to be the most appropriate dose for the treatment of persistent asthma on top of ICS therapy. While both SR doses demonstrated a modest, but statistically significant, effect on FEV_1 in asthma, the spirometric data from phase 3 trials consistently indicate that SR 2.5 has an equivalent, if not improved, bronchodilator treatment effect compared to SR 5 with similar effects on reduction of asthma exacerbations. In adolescents, efficacy results were slightly more mixed; however, SR 2.5 demonstrated statistically significant improvements in the primary endpoint of FEV_1 $peak_{(0-3)}$ in both trials and led to a decreased number of asthma exacerbations over placebo. Although only the 5 µg dose was evaluated in trials 416 and 417, which had the advantage of evaluating the greatest severity of disease for the longest duration, this patient population had fixed obstructive airway disease to the extent that would fulfill spirometric criteria for the diagnosis of COPD. As such, data from these trials play a supportive, but not decisive, role in demonstrating effectiveness of SR in asthma. Furthermore, the failure to evaluate SR 2.5 in these trials does not provide a reasonable justification for selecting SR 5 for the proposed asthma population.

6.1 Indication

The proposed dose and indication for Spiriva Respimat is (b) (4) µg once daily 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. (b) (4) .

6.1.1 Methods

In the Applicant's asthma development program, all of the Phase 3 trials were randomized, double-blind, placebo-controlled, and parallel-group in design. The efficacy review is based on a total of seven trials: five trials in adults with severe (416/417), moderate (418/419), or mild (442) asthma and two trials in adolescents with severe (456) or moderate (444) asthma.

Although the efficacy trials were relatively similar in design other than differences in asthma severity, background medications, and treatment duration as detailed in Section 5.3 and summarized in Table 18 below, it is worth highlighting a few major differences. The replicate 48-week trials in adults with severe asthma (416 and 417) only evaluated SR 5, whereas all other trials included both SR 2.5 and SR 5 treatment arms. Additionally, replicate trials 418 and 419 in adults with moderate asthma also included salmeterol HFA, a product marketed outside the U.S., as an active treatment arm. Additionally, inclusion criteria for trials 416 and 417 required subjects to possess a post-bronchodilator $FEV_1/FVC \leq 70\%$. While a degree of fixed obstruction might be expected in a portion of severe, long-standing asthma patients, a fixed FEV_1/FVC ratio is also the spirometric criterion required to make the diagnosis of COPD[9]. Table 17 lists the criteria for diagnosis of COPD as recommended in the 2015 report by the Global Initiative for Chronic Obstructive Lung Disease (GOLD).

Table 17. GOLD Criteria for Diagnosis of COPD*

Dyspnea that is:	Progressive (worsens over time)
	Characteristically worse with exercise
	Persistent
Chronic cough:	May be intermittent and may be unproductive
Chronic sputum production:	
	Any pattern of chronic sputum production may indicate COPD
History of exposure to risk factors:	
	Tobacco smoke (including popular local preparations)
	Smoke from home cooking and heating fuels
	Occupational dusts and chemicals
Family history of COPD	
Spirometry (required):	Post-bronchodilator fixed ratio of FEV1/FVC < 0.70

*COPD should be considered and spirometry performed if any of these indicators are present in an individual over age 40. While the indicators are not diagnostic themselves, the presence of multiple key indicators increases the probability of a diagnosis of COPD. Spirometry is required to establish a diagnosis of COPD.
Source: 2015 Gold Report, Table 2.1, p10

[9] www.goldcopd.org

While the Applicant has submitted a number of trials to support the proposed indication in asthma patients, their approach was untraditional. Typically, asthma development programs are encouraged/required to evaluate the full spectrum of asthma severities to inform product labeling even if approval is only for a subset of the population. Particularly for drugs that are developed as bronchodilators, this approach allows an evaluation of the optimal bronchodilator response in “naive” asthmatics who are not on background asthma medications such as ICS. A limited study in adult males with mild intermittent asthma was conducted with SHH, but no such study exists with SR. In addition, as mentioned in Section 4.4.2, most of the phase 2 dose-ranging/regimen studies were conducted concurrently with or after the phase 3 confirmatory trials. Table 18 highlights the key differences among the phase 3 efficacy trials.

Table 18. Key Differences in Phase 3 Trials

Trial	Trial Design		Demographics/Baseline Characteristics				Background meds	
	Treatment Duration	Active Treatment Arms	Age (years)	Asthma Severity	Pre-bronchodilator FEV1	Post-bronchodilator[1] FEV_1	ICS dose[2]	LABA
416/417	48 weeks	SR 5	18 to 75	Severe Persistent	---	FEV1≤ 80% and FEV1/FVC ≤ 70% of predicted normal (reversibility not required)	High	+
418/419	24 weeks	SR 2.5 SR 5 Salmeterol	18 to 75	Moderate Persistent	FEV1 ≥ 60% and ≤ 90% predicted normal	FEV1 increase of ≥12% and ≥200 mL	Medium	-
442	12 weeks	SR 2.5 SR 5	18 to 75	Mild Persistent	FEV1 ≥ 60% and ≤ 90% predicted normal	FEV1 increase of ≥12% and ≥200 mL	Low	-
444	48 weeks	SR 2.5 SR 5	12 to 17	Moderate Persistent	FEV1 ≥ 60% and ≤ 90% predicted normal	FEV1 increase of ≥12% and ≥200 mL[3]	Medium[4]	-
456	12 weeks	SR 2.5 SR 5	12 to 17	Severe Persistent	FEV1 ≥ 60% and ≤ 90% predicted normal	FEV1 increase of ≥12% and ≥200 mL[3]	High + 1 controller or Medium + 2 controllers[4]	±

Abbreviations: FEV1=Forced Expiratory Volume in 1 second, ICS=inhaled corticosteroid, LABA=long-acting beta agonist, SR=Spiriva Respimat
[1]Post-bronchodilator defined as 15-30 minutes following 4 actuations of 100 µg salbutamol/albuterol
[2]Doses based on adaptation of Global Initiative for Asthma (GINA), 2009
[3]If patients in the lower age range (12-14 years) exhibited a very small total lung volume, positive revers bility could be based solely on the relative (≥12%) post-bronchodilator response
[4]For the lower age group (12-14 years old), the inhaled corticosteroid dosing recommendations for children >5 years may have been used if appropriate
Source: Reviewer generated table based on individual study protocols

6.1.2 Demographics

Overall, the age, gender, race, and baseline lung function were similar across treatment groups within each confirmatory trial. In the adult trials, subjects were predominantly female and white with an asthma history greater than 10 years. In the adolescent trials, subjects were predominantly male and white with a mean asthma duration of 8 years.

Notably, subjects in trials 416 and 417 differed from typical asthma patients and the other clinical trial subjects in that they were all required to have fixed obstruction with relatively minimal post-bronchodilator reversibility. Additionally, compared to the other adult trials, these subjects were older with a higher incidence of past tobacco use, and virtually all were on background LABA therapy prior to entering the trial. Thus, by nature of the entry criteria, the trial populations in 416 and 417 likely included subjects who may have had COPD or Asthma-COPD overlap syndrome. This fact was also noted in an editorial response to the publication of these trials in the New England Journal of Medicine[10,11]. While total serum IgE levels and peripheral blood eosinophil counts suggest the presence of some degree of atopy in the 416 and 417 trial populations, whether or not this can be extrapolated to the presence of allergic asthma is questionable.

While there is an underrepresentation of Black/African American subjects overall since most of the study sites were outside of the U.S., the percentage of Blacks/African Americans within U.S./Canadian subjects (18%) is greater than the percentage of Blacks/African Americans within the general U.S. population (~13%).

Table 19, Table 20, Table 21, Table 22, and Table 23 below provide demographics and baseline characteristics for the treated set population in each trial.

Table 19. Demographic and Baseline Characteristics: 416 and 417

Demographic Parameters	Placebo		SR 5	
	416 N=222	417 N=234	416 N=237	417 N=219
Age (years)				
Mean (SD)	54 (13)	54 (12)	53 (12)	51 (13)
Range	18-75	19-74	19-75	19-75
Age groups, n (%)				
≤ 30 years	13 (6)	10 (4)	15 (6)	20 (9)
31-50 years	61 (27)	74 (32)	76 (32)	74 (34)
≥ 51 years	148 (67)	150 (64)	146 (62)	125 (57)

[10] Kerstjens HA, et al. Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med.* 2012 Sep 27; 367 (13): 1198-207
[11] Bel EH. Tiotropium for asthma – promise and caution. *N Engl J Med.* 2012 Sep 27; 367 (13): 1257-9

Demographic Parameters	Placebo		SR 5	
	416 N=222	417 N=234	416 N=237	417 N=219
Gender, n (%)				
Female	143 (65)	135 (58)	146 (62)	127 (58)
Race, n (%)				
White	187 (84)	196 (84)	200 (84)	176 (80)
Black/African American	11 (5)	14 (6)	9 (4)	13 (6)
Asian	23 (10)	24 (10)	27 (11)	29 (13)
Hawaiian/Pacific Islander	1 (1)	0	0	1 (1)
American Indian/Alaskan Native	0	0	1 (<1)	0
Ethnicity, n (%)				
Hispanic/Latino	4 (2)	11 (5)	4 (2)	10 (5)
Duration of asthma, n (%)				
< 1 year	0	0	0	0
1 – 9 years	5 (2)	8 (3)	7 (3)	18 (8)
10 – 19 years	39 (18)	49 (21)	41 (17)	47 (22)
≥ 20 years	178 (80)	177 (76)	189 (80)	154 (70)
Mean duration in years	31	31	32	27
Baseline lung function, pre-bronchodilator (mean)[1]				
FEV_1 (L)	1.558	1.598	1.596	1.659
FVC (L)	2.704	2.788	2.715	2.894
FEV_1/FVC (%)	58	58	60	58
Baseline FEV1 percent-predicted class, n (%)				
< 60%	130 (59)	137 (59)	133 (56)	125 (57)
60 – 80%	88 (40)	91 (39)	101 (43)	90 (41)
> 80%	4 (2)	6 (3)	3 (1)	4 (2)
Mean percent-predicted FEV_1 (%)	56	56	56	56
Post-bronchodilator reversibility (mean)[2]				
Pre-post change in FEV_1 (mL)	230	209	201	228
Percent reversibility FEV_1 (%)	16	15	14	15
FEV_1 (L)	1.759	1.780	1.767	1.847
FVC (L)	2.966	3.055	2.953	3.170
FEV_1/FVC (%)	59	59	60	58
Smoking history, n (%)				
Ex-smoker	48 (22)	56 (24)	55 (23)	61 (28)
Mean pack years (SD)	5 (3)	5 (3)	6 (3)	5 (3)
Laboratory results (mean, median)				
Total serum IgE (kU/L)	296, 131	282, 136	411, 176	310, 124
Blood eosinophil count (cells/µL)	378, 274	315, 260	429, 290	360, 280
Concomitant medications[3]				
Oral corticosteroids	36 (16)	43 (18)	34 (14)	41 (19)
LABA	213 (96)	231 (99)	230 (97)	212 (97)
Anticholinergics	21 (10)	24 (10)	21 (9)	24 (11)
Xanthines	54 (24)	35 (15)	53 (22)	38 (17)
Leukotriene modifiers	61 (28)	46 (20)	60 (26)	36 (16)
Omalizumab	10 (5)	14 (6)	6 (3)	6 (3)

[1]Measured 10 minutes prior to inhalation of 4 puffs salbutamol at Visit 2

Demographic Parameters	Placebo		SR 5	
	416 N=222	417 N=234	416 N=237	417 N=219

[2]Measured 15-30 minutes after inhalation of 4 puffs salbutamol at Visit 1
[3]Within 3 months of Visit 1
Source: Module 5.3.5.1, CSR, Tables 11.2.5.1:1, 11.2.5.2:1, 15.1.4:1, 15.1.4:4, 15.1.4:10

Table 20. Demographic and Baseline Characteristics: 418 and 419

Demographic Parameters	Placebo		SR 2.5		SR 5		Salmeterol	
	418 N=269	419 N=254	418 N=262	419 N=257	418 N=264	419 N=253	418 N=275	419 N=266
Age (years)								
Mean (SD)	43 (13)	43 (13)	44 (13)	43 (13)	44 (13)	44 (13)	43 (13)	42 (13)
Range	18-75	18-75	18-72	19-74	18-73	19-74	18-74	18-71
Age groups, n (%)								
≤ 30 years	54 (20)	54 (21)	49 (19)	49 (19)	35 (13)	43 (17)	54 (20)	65 (24)
31-50 years	144 (54)	124 (49)	120 (46)	135 (53)	142 (54)	133 (53)	145 (52)	131 (49)
≥ 51 years	71 (26)	76 (30)	93 (35)	73 (28)	87 (33)	77 (30)	76 (28)	70 (26)
Gender, n (%)								
Female	166 (62)	145 (57)	156 (60)	160 (62)	154 (58)	146 (58)	159 (58)	153 (58)
Race, n (%)								
White	128 (48)	118 (47)	130 (50)	123 (48)	121 (46)	119 (47)	139 (51)	127 (48)
Black/African American	14 (5)	13 (5)	7 (3)	10 (4)	13 (5)	9 (4)	7 (3)	8 (3)
Asian	111 (41)	108 (43)	110 (42)	110 (43)	116 (44)	109 (43)	115 (42)	114 (43)
Hawaiian/Pacific Islander	1 (<1)	0	0	2 (1)	0	0	0	0
American Indian/Alaskan Native	15 (6)	15 (6)	15 (6)	12 (5)	14 (5)	16 (6)	14 (5)	17 (6)
Ethnicity, n (%)								
Hispanic/Latino	34 (13)	20 (8)	33 (13)	22 (9)	34 (13)	24 (10)	33 (12)	25 (9)
Duration of asthma, n (%)								
< 1 year	7 (3)	3 (1)	7 (3)	9 (4)	9 (3)	8 (3)	9 (3)	5 (2)
1 – 9 years	51 (19)	53 (21)	54 (21)	53 (21)	40 (15)	48 (19)	51 (19)	62 (23)
10 – 19 years	80 (30)	56 (22)	57 (22)	51 (20)	70 (27)	56 (22)	68 (25)	69 (26)
≥ 20 years	131 (49)	142 (56)	144 (55)	144 (56)	145 (55)	141 (56)	147 (54)	130 (49)
Mean duration in years	20	22	22	22	23	23	21	20
Baseline lung function, pre-bronchodilator (mean)[1]								
FEV_1 (L)	2.251	2.268	2.247	2.284	2.154	2.257	2.305	2.367
FVC (L)	3.434	3.503	3.399	3.477	3.379	3.449	3.491	3.530
FEV_1/FVC (%)	66	65	67	66	65	66	66	68
Baseline FEV1 percent-predicted class, n (%)[1]								
< 60%	23 (9)	26 (10)	28 (11)	18 (7)	33 (13)	21 (8)	29 (11)	24 (9)

Demographic Parameters	Placebo		SR 2.5		SR 5		Salmeterol	
	418 N=269	419 N=254	418 N=262	419 N=257	418 N=264	419 N=253	418 N=275	419 N=266
60 – 80%	163 (61)	145 (57)	139 (53)	146 (57)	157 (60)	146 (58)	148 (54)	140 (53)
> 80%	83 (31)	82 (32)	95 (36)	93 (36)	73 (28)	86 (34)	98 (36)	101 (38)
Mean percent-predicted FEV_1 (%)	75	75	75	76	73	75	75	77
Post-bronchodilator reversibility (mean)[2]								
Pre-post change in FEV_1 (mL)	488	471	508	495	459	453	498	489
Percent reversibility FEV_1 (%)	23	22	24	23	22	21	23	22
FEV_1 (L)	2.670	2.689	2.688	2.684	2.591	2.626	2.711	2.747
FVC (L)	3.748	3.799	3.731	3.756	3.710	3.725	3.811	3.802
FEV_1/FVC (%)	72	71	73	72	70	71	72	73
Smoking history, n (%)								
Ex-smoker	28 (10)	42 (17)	38 (15)	44 (17)	39 (15)	58 (23)	42 (15)	53 (20)
Mean pack years (SD)	5 (3)	4 (3)	4 (3)	4 (3)	5 (3)	5 (3)	4 (3)	4.0 (3)
Laboratory results (mean, median)								
Total serum IgE (kU/L)	429, 179	687, 185	351, 143	643, 171	501, 172	448, 170	427, 144	501, 170
Blood eosinophil count (cells/µL)	296, 230	362, 280	303, 258	343, 270	329, 265	310, 240	301, 240	1210, 280
Concomitant medications[3]								
Oral corticosteroids	4 (2)	8 (3)	3 (1)	6 (2)	5 (2)	8 (3)	3 (1.1)	11 (4)
LABA	152 (57)	169 (67)	144 (55)	176 (69)	142 (54)	168 (66)	148 (54)	177 (67)
Anticholinergics	4 (2)	5 (2)	9 (3)	7 (3)	6 (2)	6 (2)	3 (1)	5 (2)
Xanthines	12 (5)	22 (9)	12 (5)	22 (9)	12 (5)	26 (10)	13 (5)	15 (6)
Leukotriene modifiers	26 (10)	27 (11)	26 (10)	27 (11)	32 (12)	22 (9)	30 (11)	22 (8)
Omalizumab	0	0	0	0	0	0	0	0

[1]Measured 10 minutes prior to inhalation of 4 puffs salbutamol at Visit 2
[2]Measured 15-30 minutes after inhalation of 4 puffs salbutamol at Visit 1
[3]Within 3 months of Visit 1
Source: Module 5.3.5.1, CSR, Tables 11.2.5.1:1, 11.2.5.2:1, 15.1.4:1, 15.1.4:4, 15.1.4:10

Table 21. Demographic and Baseline Characteristics: 442

Demographic Parameters	Placebo N=155	SR 2.5 N=154	SR 5 N=155
Age (years)			
Mean (SD)	43 (12)	44 (14)	42 (13)
Range	18-73	18-71	18-74
Age groups, n (%)			
≤ 30 years	24 (15)	31 (20)	32 (21)
31-50 years	88 (57)	70 (46)	82 (53)
≥ 51 years	43 (28)	53 (34)	41 (26)
Gender, n (%)			

Demographic Parameters	Placebo N=155	SR 2.5 N=154	SR 5 N=155
Female	103 (67)	82 (53)	96 (62)
Race, n (%)			
White	119 (77)	121 (79)	122 (79)
Black/African American	1 (0.6)	0	0
Asian	30 (20)	26 (17)	29 (19)
American Indian/Alaskan Native	5 (3)	7 (5)	4 (3)
Ethnicity, n (%)			
Hispanic/Latino	11 (7)	16 (10)	11 (7)
Duration of asthma, n (%)			
< 1 year	5 (3)	8 (5)	4 (3)
1 – 9 years	48 (31)	46 (30)	49 (32)
10 – 19 years	51 (33)	41 (27)	50 (32)
≥ 20 years	51 (33)	59 (38)	52 (34)
Mean duration in years	16	17	15
Baseline lung function, pre-bronchodilator (mean)[1]			
FEV_1 (L)	2.376	2.401	2.482
FVC (L)	3.480	3.566	3.579
FEV_1/FVC (%)	68	67	70
Baseline FEV1 % predicted class, n (%)[1]			
< 60%	12 (8)	11 (7)	2 (1)
60 – 80%	76 (49)	87 (57)	79 (51)
> 80%	67 (43)	56 (36)	74 (48)
Mean percent-predicted FEV_1 (%)	78	76	80
Post-bronchodilator reversibility (mean)[2]			
Pre-post change in FEV_1 (mL)	544	560	563
Percent reversibility FEV_1 (%)	25	25	25
FEV_1 (L)	2.790	2.871	2.893
FVC (L)	3.779	3.884	3.887
FEV_1/FVC (%)	74	74	75
Smoking history, n (%)			
Ex-smoker	26 (17)	23 (15)	33 (21)
Mean pack years (SD)	6 (3)	4 (3)	4 (3)
Laboratory results (mean, median)			
Total serum IgE (kU/L)	301, 120	289, 148	325, 111
Blood eosinophil count (cells/µL)	5986, 227	6456, 244	7309, 240
Concomitant Medications[3]			
Oral corticosteroids	2 (1)	0	1 (1)
LABA	25 (16)	20 (13)	20 (13)
Anticholinergics	7 (5)	8 (5)	8 (5)
Xanthines	3 (2)	2 (1)	3 (2)
Leukotriene modifiers	6 (4)	3 (2)	0
Omalizumab	0	0	0

[1]Measured 10 minutes prior to inhalation of 4 puffs salbutamol at Visit 2
[2]Measured 15-30 minutes after inhalation of 4 puffs salbutamol at Visit 1
[3]Within 3 months of Visit 1
Source: Module 5.3.5.1, CSR, Tables 11.2.1:1, 11.2.5.1:1, 11.2.5.2:1, 15.1.4.1:1, 15.1.4.4:1, 15.1.4.5:3

Table 22. Demographic and Baseline Characteristics: 444

Demographic Parameters	Placebo N=138	SR 2.5 N=125	SR 5 N=134
Age (years)			
Mean (SD)	14 (2)	14 (2)	15 (2)
Range	12-17	11-17	12-17
Age groups, n (%)			
< 12 years	0	1 (1)	0
12-14 years	76 (55)	72 (58)	67 (50)
15-17 years	62 (45)	52 (42)	67 (50)
Gender, n (%)			
Female	50 (36)	44 (35)	45 (34)
Race, n (%)			
White	126 (92)	118 (95)	124 (93)
Black/African American	5 (4)	5 (4)	4 (3)
Asian	6 (4)	2 (2)	5 (4)
American Indian/Alaskan Native	1 (1)	0	1 (1)
Ethnicity, n (%)			
Hispanic/Latino	13 (9)	15 (12)	14 (10)
Duration of asthma, n (%)			
< 1 year	6 (4)	3 (2)	4 (3)
1 – 2 years	19 (14)	13 (11)	16 (12)
≥ 3 years	113 (82)	109 (88)	114 (85)
Mean duration in years	8	8	8
Baseline lung function, pre-bronchodilator (mean)[1]			
FEV_1 (L)	2.736	2.680	2.821
FVC (L)	3.570	3.461	3.639
FEV_1/FVC (%)	77	78	78
Baseline FEV1 % predicted class, n (%)[1]			
< 60%	1 (1)	2 (2)	1 (1)
60 – 80%	49 (36)	54 (43)	51 (38)
> 80%	88 (64)	69 (55)	82 (61)
Mean percent-predicted FEV_1 (%)	83	82	83
Post-bronchodilator reversibility (mean)[2]			
Pre-post change in FEV_1 (mL)	657	663	689
Percent reversibility FEV_1 (%)	26	27	27
FEV_1 (L)	3.210	3.200	3.313
FVC (L)	3.905	3.882	3.981
FEV_1/FVC (%)	83	83	84
Smoking history, n (%)			
Current/ex-smoker	1 (1)	0	0
Second hand smoke exposure	18 (13)	10 (8)	16 (12)
Laboratory results (mean, median)			
Total serum IgE (kU/L)	640, 301	685, 399	611, 289
Blood eosinophil count (cells/µL)	347, 252	363, 289	349, 280
Concomitant Medications[3]			
Oral corticosteroids	1 (1)	0	1 (1)
LABA	39 (28)	35 (28)	41 (31)

Demographic Parameters	Placebo N=138	SR 2.5 N=125	SR 5 N=134
Anticholinergics	1 (1)	3 (2)	2 (2)
Xanthines	1 (1)	3 (2)	0
Leukotriene modifiers	18 (13)	12 (10)	17 (13)
Omalizumab	0	0	0

[1]Measured 10 minutes prior to inhalation of 4 puffs salbutamol at Visit 2
[2]Measured 15-30 minutes after inhalation of 4 puffs salbutamol at Visit 1
[3]Within 3 months of Visit 1
Source: Module 5.3.5.1, CSR, Tables 11.2.1:1, 11.2.5.1:1, 11.2.5.2:1, 15.1.4.1:1, 15.1.4.4:1, 15.1.4.5:3

Table 23. Demographic and Baseline Characteristics: 456

Demographic Parameters	Placebo N=135	SR 2.5 N=127	SR 5 N=130
Age (years)			
Mean (SD)	14 (2)	14 (2)	14 (2)
Range	12-17	12-17	12-17
Age groups, n (%)			
12-14 years	74 (55)	66 (52)	71 (55)
15-17 years	61 (45)	61 (48)	59 (45)
Gender, n (%)			
Female	56 (42)	47 (37)	47 (36)
Race, n (%)			
White	126 (93)	123 (97)	122 (94)
Black/African American	4 (3)	2 (2)	2 (2)
Asian	3 (2)	2 (2)	5 (4)
American Indian/Alaskan Native	2 (2)	0	1 (1)
Ethnicity, n (%)			
Hispanic/Latino	25 (19)	18 (14)	25 (19)
Duration of Asthma, n (%)			
< 1 year	3 (2)	2 (2)	5 (4)
1 – 2 years	15 (11)	12 (9)	24 (19)
≥ 3 years	117 (87)	113 (89)	101 (78)
Mean duration in years	8	8	7
Baseline lung function, pre-bronchodilator (mean)[1]			
FEV_1 (L)	2.451	2.546	2.580
FVC (L)	3.280	3.280	3.386
FEV_1/FVC (%)	75	79	77
Baseline FEV1 percent-predicted class, n (%)[1]			
< 60%	5 (4)	3 (2)	4 (3)
60 – 80%	71 (53)	57 (45)	68 (52)
> 80%	59 (44)	67 (53)	58 (45)
Mean percent-predicted FEV_1	79	80	79
Post-bronchodilator reversibility (mean)[2]			
Pre-post change in FEV_1 (mL)	664	706	678
Percent reversibility FEV_1 (%)	29	29	27
FEV_1 (L)	2.975	3.142	3.157
FVC (L)	3.648	3.772	3.840
FEV_1/FVC (%)	82	84	83

Demographic Parameters	Placebo N=135	SR 2.5 N=127	SR 5 N=130
Smoking history, n (%)			
Current/ex-smoker	0	0	0
Second hand smoke exposure	6 (4)	8 (6)	10 (8)
Laboratory results (mean, median)			
Total serum IgE (kU/L)	503, 215	597, 375	551, 314
Blood eosinophil count (cells/µL)	8344, 370	1737, 320	520, 310
Concomitant Medications[3]			
Oral corticosteroids	2 (2)	0	2 (2)
LABA	117 (87)	101 (80)	108 (83)
Anticholinergics	4 (3)	0	1 (1)
Xanthines	10 (7)	7 (6)	8 (6)
Leukotriene modifiers	109 (81)	104 (82)	102 (79)
Omalizumab	0	0	1 (1)

[1]Measured 10 minutes prior to inhalation of 4 puffs salbutamol at Visit 2
[2]Measured 15-30 minutes after inhalation of 4 puffs salbutamol at Visit 1
[3]Within 3 months of Visit 1
Source: Module 5.3.5.1, CSR, Tables 11.2.1:1, 11.2.5.1:1, 11.2.5.2:1, 15.1.4.4:1, 15.1.4.5:1, 15.1.4.5:2, 15.1.4.5:3, 15.1.4.5:4

6.1.3 Subject Disposition

In the seven trials, a total of 4,270 subjects were randomized, of whom 4,265 were treated with at least one dose of trial medication. A majority of subjects (94%) completed the trials. Overall, the most common reasons for premature discontinuation of trial medication were withdrawal of consent/refusal to continue trial medication, other, and adverse events. For the most part, early dropouts categorized as withdrawal of consent or other were due to social circumstances that interfered with trial participation and follow-up. Although dropouts categorized as lack of efficacy were relatively rare, there were fewer discontinuations due to an adverse event of worsening asthma in the active treatment groups. Table 24, Table 25, Table 26, Table 27, and Table 28 depict subject disposition with primary reason for discontinuation for each of the seven trials. Treatment compliance captured by daily electronic diary entries is summarized below the corresponding table for each trial.

Table 24. Subject Disposition: 416 and 417

	Placebo		SR 5	
	416	417	416	417
Randomized	222	234	237	219
Treated, n (%)	222 (100)	234 (100)	237 (100)	219 (100)
Completed trial medication	202 (91)	203 (87)	211 (89)	198 (90)
Prematurely discontinued	20 (9)	31 (13)	26 (11)	21 (10)
Adverse events	6 (3)	8 (3)	6 (2)	2 (1)
Worsening of asthma	3 (1)	5 (2)	2 (1)	1 (1)
Worsening of other pre-existing disease	0	0	0	0
Other AE	3 (1)	3 (1)	4 (2)	1 (1)
Lack of efficacy	0	0	1 (<1)	1 (1)
Non-compliance with protocol	3 (1)	4 (2)	3 (1)	2 (1)

	Placebo		SR 5	
	416	417	416	417
Lost to follow-up	1 (1)	2 (1)	1 (<1)	0
Refusal to continue trial medication	3 (1)	12 (5)	8 (3)	7 (3)
Other	7 (3)	5 (2)	7 (3)	9 (4)
Source: CSR 205.416 and 205.417, Tables 10.1:1				

Treatment Compliance in Trials 416 and 417:

The overall mean and median treatment compliance was high in both trials: 88% and 94% in trial 416 and 89% and 94% in trial 417; there was no substantial difference between SR and placebo treatment groups. Within each trial, 9% of all patients were <70% compliant.

Table 25. Subject Disposition: 418 and 419

	Placebo		SR 2.5		SR 5		Salmeterol	
	418	419	418	419	418	419	418	419
Randomized	269	259	262	258	265	254	275	266
Treated, n (%)	269 (100)	254 (100)	262 (100)	257 (100)	264 (100)	253 (100)	275 (100)	266 (100)
Completed trial medication	248 (92)	240 (95)	249 (95)	245 (95)	241 (91)	240 (95)	260 (95)	249 (94)
Prematurely discontinued	21 (8)	14 (6)	13 (5)	12 (5)	23 (9)	13 (5)	15 (6)	17 (6)
Adverse events	8 (3)	5 (2)	4 (2)	2 (1)	8 (3)	2 (1)	3 (1)	7 (3)
Worsening of asthma	4 (2)	3 (1)	0	1 (<1)	3 (1)	0	1 (<1)	3 (1)
Worsening of other pre-existing disease	1 (<1)	0	1 (<1)	0	1 (<1)	0	1 (<1)	1 (<1)
Other AE	3 (1)	2 (1)	3 (1)	1 (<1)	4 (2)	2 (1)	1 (<1)	3 (1)
Lack of efficacy	1 (<1)	0	0	0	0	0	0	0
Non-compliance with protocol	2 (1)	0	2 (1)	2 (1)	2 (1)	1 (<1)	0	2 (1)
Lost to follow-up	0	4 (2)	1 (<1)	1 (<1)	1 (<1)	2 (1)	3 (1)	2 (1)
Consent withdrawn (not due to AE)	4 (2)	2 (1)	1 (<1)	3 (1)	3 (1)	3 (1)	2 (1)	3 (1)
Other	6 (2)	3 (1)	5 (2)	4 (2)	9 (3)	5 (2)	7 (3)	3 (1)
Source: CSR 205.418 and 205.419, Tables 10.1:1								

Treatment Compliance in Trials 418 and 419:

The overall mean and median treatment compliance was high at 88% and 94%, respectively, for both trials with similar findings among individual treatment groups. Altogether, 81% of the patients were between 80% and 100% compliant during both trials while 11% in trial 418 and 9% in trial 419 were <70% compliant.

Table 26. Subject Disposition: 442

	Placebo	SR 2.5	SR 5
Randomized	156	154	155
Treated, n (%)	155 (100)	154 (100)	155 (100)
Completed trial medication	154 (99.4)	149 (96.8)	152 (98.1)
Prematurely discontinued	1 (1)	5 (3)	3 (2)

	Placebo	SR 2.5	SR 5
Adverse events	0	2 (1)	1 (1)
Worsening of asthma	0	2 (1)	0
Worsening of other pre-existing disease	0	0	0
Other AE	0	0	1 (1)
Lack of efficacy	0	0	0
Non-compliance with protocol	0	0	1 (1)
Lost to follow-up	0	0	0
Consent withdrawn (not due to AE)	1 (1)	2 (1)	0
Other	0	1 (1)	1 (1)

Source: CSR 205.442, Table 10.1:1

Treatment Compliance in Trial 442:

The overall mean and median treatment compliance was high (91 and 96%, respectively) and similar across treatment groups. As expected, the majority of patients (92-96% from each treatment group) were between 70% and 100% compliant during the trial. While a total of 27 patients (6%) had <70% treatment compliance according to their e-Diary entries, a review of the returned Respimat inhalers revealed that 10 of these patients had taken trial drug as required but failed to record the data in their diaries.

Table 27. Subject Disposition: 444

	Placebo	SR 2.5	SR 5
Randomized	138	125	135
Treated, n (%)	138 (100)	125 (100)	134 (100)
Completed trial medication	132 (96)	115 (92)	129 (96)
Prematurely discontinued	6 (4)	10 (8)	5 (4)
Adverse events	2 (2)	0	0
Worsening of asthma	2 (2)	0	0
Worsening of other pre-existing disease	0	0	0
Other AE	0	0	0
Lack of efficacy	0	1 (1)	0
Non-compliance with protocol	3 (2)	0	1 (1)
Lost to follow-up	0	0	0
Consent withdrawn (not due to AE)	0	4 (3)	1 (1)
Other	1 (1)	5 (4)	3 (2)

Source: CSR 205.444, Table 10.1:1

Treatment Compliance in Trial 444:

Overall, median treatment compliance as recorded in the e-Diary was 76% and was lower in the SR 5 group (72%) than in the SR 2.5 and placebo groups (78-79%). Mean compliance was slightly lower than median compliance, and ranged from 66% in the SR 5 group to 72% in the placebo group. Less than half of all patients (44%) were between 80% and 100% compliant, while over a quarter of patients (26-31% for each treatment group) were <60% compliant. Higher levels of compliance were observed based on the dose indicator data with 305 of the 397 patients (77%) demonstrating overall medication intake compliance of ≥80% for the 48-week treatment period.

Table 28. Subject Disposition: 456

	Placebo	SR 2.5	SR 5
Randomized	135	127	130
Treated, n (%)	135 (100)	127 (100)	130 (100)
Completed trial medication	132 (98)	126 (99)	130 (100)
Prematurely discontinued	3 (2)	1 (1)	0
Adverse events	1 (1)	0	0
Worsening of asthma	0	0	0
Worsening of other pre-existing disease	0	0	0
Other AE	1 (1)	0	0
Lack of efficacy	0	0	0
Non-compliance with protocol	2 (2)	0	0
Lost to follow-up	0	0	0
Consent withdrawn (not due to AE)	0	0	0
Other	0	1 (1)	0

Source: CSR 205.456, Table 10.1:1

Treatment Compliance in Trial 456:
Median treatment compliance ranged from 86% for the SR 5 group to 89% for the SR 2.5 and placebo groups, while mean treatment compliance was slightly lower, ranging between 80% and 83% for all treatment groups. Although the majority of patients (67%) had compliance of ≥80%, 9-10% of patients from each treatment group reported compliance <60%. However, dose indicator data from returned Respimat devices suggest a higher level of compliance with 368 of the 392 patients (94%) in the study demonstrating ≥80% overall compliance for the 12 week treatment period.

6.1.4 Analysis of Co-Primary Endpoints: Peak and Trough FEV_1

Each of the five confirmatory trials evaluated FEV_1 $peak_{(0-3)}$ and trough FEV_1 as either co-primary or primary and key secondary endpoints. In either case, FEV_1 $peak_{(0-3)}$ was always the first co-primary or primary endpoint. The FEV_1 $peak_{(0-3)}$ was the maximum FEV_1 measurement within the first 3 hours after dosing. Trough FEV_1 was the pre-dose FEV_1 measurement obtained 10 minutes before the last administration of randomized treatment. The peak or trough FEV_1 response was defined as the difference between the peak or trough FEV_1 measured at the primary analysis time point and the peak or trough FEV_1 measured at baseline. Baseline was defined as the FEV_1 measured 10 minutes before the first dose of trial medication at Visit 2.

Results from each of the trials are shown in Table 29. With the exception of the 48-week trials (416, 417, 444), which were analyzed at 24 weeks, the primary endpoint analysis was performed at the end of treatment. Primary analyses were conducted using the Full Analysis Set (FAS) population, defined as any subject who received at least one dose of trial medication and had at least one efficacy measurement while on treatment.

Table 29. Peak$_{(0-3)}$ and Trough FEV$_1$ in Adults (FAS population)

Trial	Background Medication	Treatment	N	Adjusted mean FEV$_1$ Peak$_{(0-3)}$		Adjusted mean Trough FEV$_1$	
				Δ from baseline in mL (SE)	Difference vs placebo (95% CI)	Δ from baseline in mL (SE)	Difference vs placebo (95% CI)
Week 24							
416	High-dose ICS + LABA	Placebo	211	315 (26)		56 (25)	
		SR 5	217	401 (25)	86 (20, 152) p=0.011	144 (24)	88 (27, 149) p=0.005
417	High-dose ICS + LABA	Placebo	218	248 (24)		44 (22)	
		SR 5	205*	401 (25)	154 (91, 217) p<0.001	155 (23)	111 (53, 169) p<0.001
418	Medium-dose ICS	Placebo	250	53 (21)		-36 (22)	
		SR 2.5	247	289 (21)	236 (181, 291) p<0.001	148 (22)	185 (126, 244) p<0.001
		SR 5	241	250 (21)	198 (142, 253) p<0.001	115 (22)	152 (92, 211) p<0.001
		Salmeterol	259	266 (20)	213 (158, 267) p<0.001	86 (22)	123 (64, 181) p<0.001
419	Medium-dose ICS	Placebo	242	75 (20)		-12 (21)	
		SR 2.5	245	287 (20)	211 (159, 264) P<0.001	164 (21)	176 (120, 233) p<0.001
		SR 5	240	244 (20)	169 (116, 222) p<0.001	121 (21)	133 (76, 190) p<0.001
		Salmeterol	251	252 (19)	176 (124, 229) p<0.001	94 (21)	106 (50, 162) p<0.001
Week 12							
442	Low-dose ICS	Placebo	154	134 (26)		15 (26)	
		SR 2.5	151	293 (26)	159 (88, 230) p<0.001	125 (26)	110 (38, 182) p=0.003
		SR 5	152	262 (26)	128 (57, 199) p<0.001	137 (27)	122 (49, 194) p=0.001

Abbreviations: FAS=Full Analysis Set, SE=standard error, ICS=inhaled corticosteroid, LABA=long-acting beta-agonist, CI=confidence interval, SR=Spiriva Respimat
*N for trough FEV1=204
Source: CSR 205.416, 205.417, 205.418, 205.419, Tables 11.4.1.1.1:1; CSR 205.442, Tables 11.4.1.1.1:1 and 11.4.1.2.1:1; confirmed by statistical reviewer Dr. Kiya Hamilton

Across trials, there is a modest, but statistically significant, treatment effect of both SR 5 and SR 2.5 over placebo. Given concerns that the trial populations in 416 and 417 may actually have included subjects with COPD, for which SR 5 has already demonstrated

efficacy, the key efficacy results in adults known to have asthma are derived from trials 418, 419, and 442. In these three trials which evaluated two doses of SR, the lower 2.5 µg dose numerically outperforms the higher 5 µg dose on FEV_1 $peak_{(0-3)}$ consistently and trough FEV_1 for all but one trial. In adolescent trials 444 and 456, efficacy results based on peak and trough FEV_1 were more mixed (Table 30). In trial 456 in severe asthma, peak and trough FEV_1 were again numerically better and statistically significant in the lower SR 2.5 treatment group while the FEV_1 response with SR 5 was not significantly different than placebo. In trial 444 in moderate asthma, normal dose ordering was observed with numerically better results in the SR 5 group compared with SR 2.5, although both doses were significantly different from placebo in terms of the primary endpoint, FEV_1 $peak_{(0-3)}$. For trough FEV_1, which was a key secondary endpoint, only the higher SR 5 dose demonstrated a statistically significant difference from placebo. Overall, the treatment effect size on FEV_1 was consistently greater with SR 2.5 than SR 5 and slightly lower in adolescents as compared to adults with comparable asthma severity.

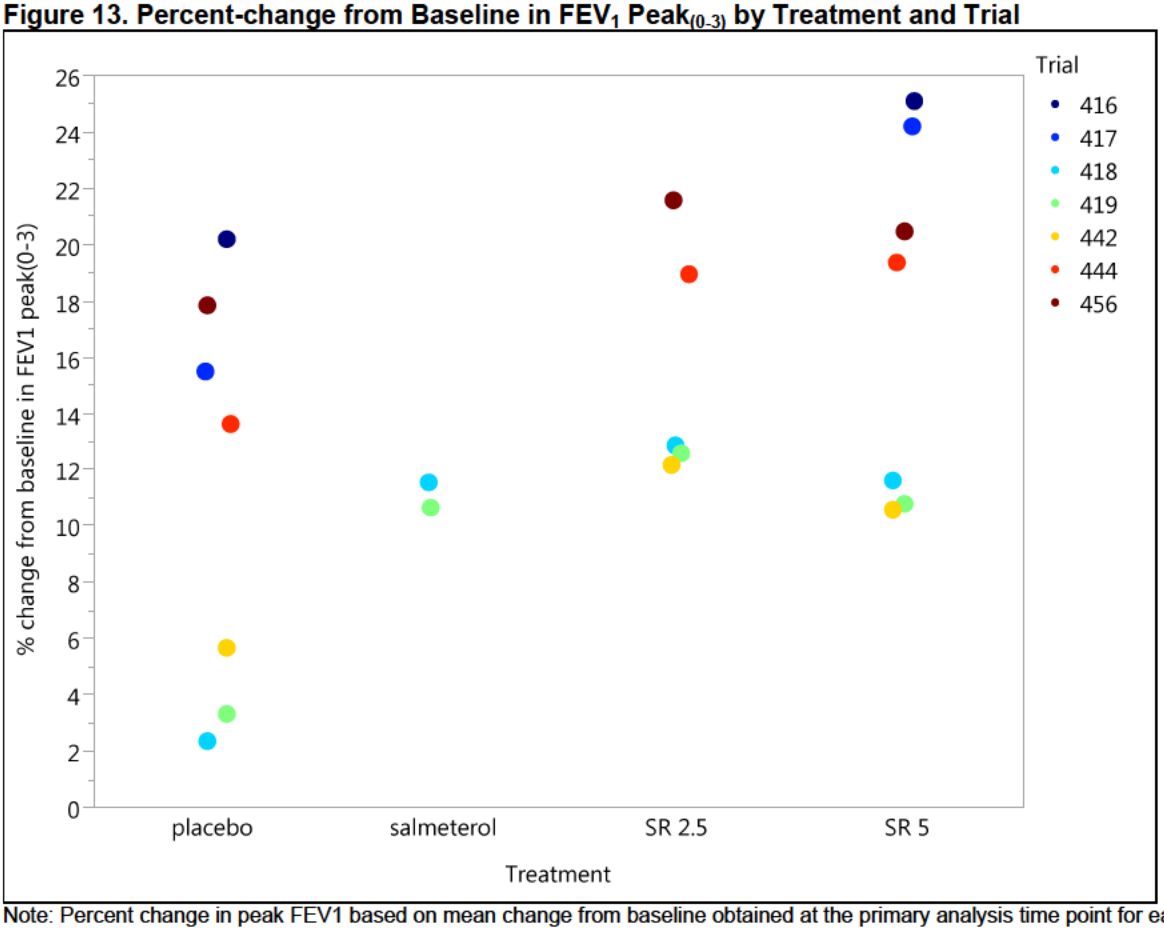
Table 30. $Peak_{(0-3)}$ and Trough FEV_1 in Adolescents (FAS population)

Trial	Background Medication	Treatment	N	Adjusted mean FEV_1 $Peak_{(0-3)}$		Adjusted mean Trough FEV_1	
				Δ from baseline in mL (SE)	Difference vs placebo (95% CI)	Δ from baseline in mL (SE)	Difference vs placebo (95% CI)
Week 24							
444	Medium-dose ICS	Placebo	137	373 (37)		283 (40)	
		SR 2.5	120*	507 (40)	134 (34, 234) p=0.009	367 (44)	84 (-25, 194) p=0.131
		SR 5	131	547 (38)	174 (76, 272) p<0.001	400 (41)	117 (10, 223) p=0.032
Week 12							
456	High-dose ICS + 1 controller OR medium-dose ICS + 2 controllers	Placebo	132	438 (45)		230 (48)	
		SR 2.5	126	550 (46)	111 (2, 220) p=0.046	345 (48)	115 (0, 231) p=0.051
		SR 5	130	528 (45)	90 (-19, 198) p=0.104	284 (48)	54 (-61, 168) p=0.361

Abbreviations: FAS=Full Analysis Set, SE=standard error, ICS=inhaled corticosteroid, LABA=long-acting beta-agonist, CI=confidence interval, SR=Spiriva Respimat
*N for trough FEV1=119
Source: CSR 205.444 and 205.456, Tables 11.4.1.1.1:1 and 11.4.1.2.1:1; confirmed by statistical reviewer, Dr. Kiya Hamilton

The figure below presents the primary outcome in a slightly different manner as the percent change from baseline in mean FEV_1 $peak_{(0-3)}$ measurements at the time point of the primary endpoint analysis for each trial. The peak FEV_1 increased between 11-25% over baseline in the SR treatment groups, representing a treatment difference of 5-10% over placebo.

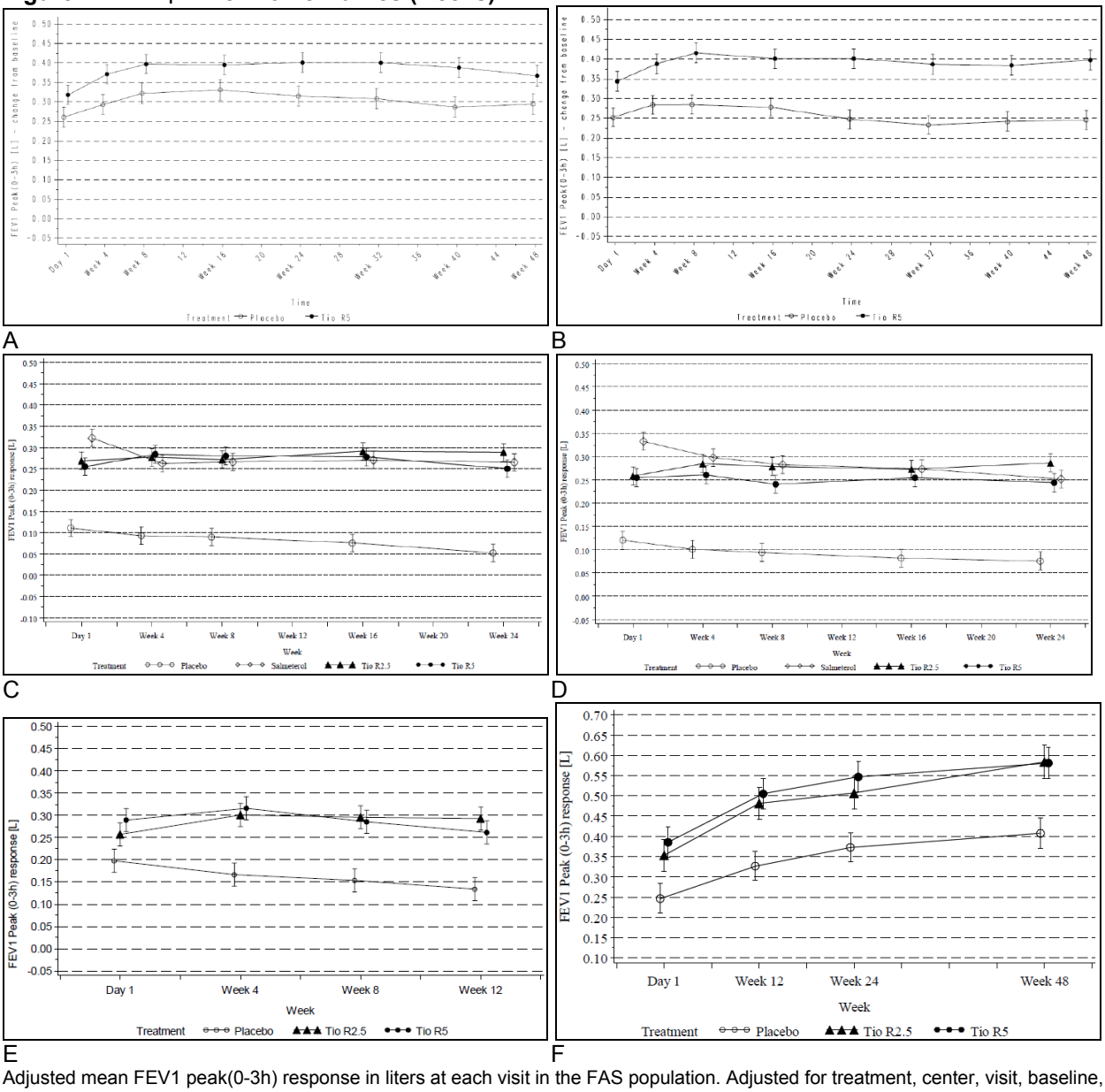
Figure 13. Percent-change from Baseline in FEV_1 $Peak_{(0-3)}$ by Treatment and Trial



Note: Percent change in peak FEV1 based on mean change from baseline obtained at the primary analysis time point for each trial
Source: Reviewer generated figure using JMP

In all but one of the trials that evaluated two SR doses, the lower 2.5 µg dose numerically outperforms the higher 5 µg dose by roughly 30-40 mL, which translates to an approximate 20% loss of the treatment effect with the higher 5 µg dose. Even in the trial in which normal dose ordering is observed (Trial 444), both doses demonstrate a statistically significant difference from placebo with regard to peak $FEV_{1(0-3)}$. Although this reversed dose ordering was not observed in phase 2 dose-ranging studies, those studies were smaller in size and shorter in duration. One possible explanation is that many of the phase 2 studies were limited to 4 week treatment periods. Based on the FEV_1 time profile curves in the longer phase 3 trials, it appears to take at least 4 weeks for the full treatment effect to be observed (Figure 14). While there is no clear explanation for the slightly better pulmonary function results seen with the 2.5 µg dose, the consistency of this trend in the phase 3 trials at a minimum suggests that the two doses are equally effective with regard to bronchodilator activity.

Figure 14. FEV_1 Time Profile Curves (weeks)



Adjusted mean FEV1 peak(0-3h) response in liters at each visit in the FAS population. Adjusted for treatment, center, visit, baseline, treatment by visit and baseline by visit.
A=Trial 416, B=Trial 417, C=Trial 418, D=Trial 419, E=Trial 442, F=Trial 444
Sources: CSR 205.416 and 205.417, Figures 11.4.1.2.2:3; CSR 205.418 and 205.419, Figures 11.4.1.3.1:1; CSR 205.442, Figure 11.4.1.2.3:1; CSR 205.444, Figure 11.4.1.3.1:1

Unlike β2-agonists which have long-been established as bronchodilators in asthma, a similar beneficial role for anticholinergics in asthma has not yet been clearly demonstrated. Due to the modest benefit of SR on FEV_1, an evaluation of the asthma exacerbations in this program is important to establishing a clinically meaningful benefit of SR for asthma, particularly given that trough FEV_1 is considered a surrogate measure of efficacy for the reduction of asthma exacerbations. Although the Applicant pre-

specified the time to first severe asthma exacerbation as a primary analysis for the pooled trial data from 416 and 417, exacerbations were also captured as secondary endpoints in the individual phase 3 trials and thus will be discussed in the following section.

6.1.5 Analysis of Secondary Endpoints: Asthma Exacerbations

Across trials, asthma exacerbations were defined in the protocol as follows:

- An episode of progressive increase in one or more asthma symptoms, like shortness of breath, cough, wheezing, or chest tightness, or some combination of these symptoms. Respiratory distress is common. The symptoms should be outside the patient's usual range of day-to-day asthma and should last for at least two consecutive days

And/or

- A decrease of patient's best morning PEF of ≥30% from the patient's mean morning PEF for at least two consecutive days. Relevant PEF deteriorations are marked on the AM3 data reports downloaded at each visit. During the treatment period, mean morning PEF was defined as the mean value of all best morning PEF values obtained during the complete screening period including the morning of Visit 2.

"Severe" exacerbations were defined as the subset of exacerbations requiring initiation of treatment with systemic (including oral) corticosteroids or doubling of current oral corticosteroid dose for at least 3 days. Courses of corticosteroids separated by 1 week or more were treated as separate exacerbation events.

An asymptomatic decrease in PEF was considered an asthma exacerbation per protocol regardless of being accompanied by asthma symptoms, need for additional asthma medication, or if considered medically relevant or not. At every AM3 download, the report included an alert section summarizing all relevant PEF-decreases that occurred since the last visit which the investigator reviewed with the patient to determine which alerts were valid. If a respiratory tract infection without asthma worsening was the reason of the PEF decrease (e.g., bronchitis), then this was documented as an AE, but not as an asthma exacerbation per protocol.

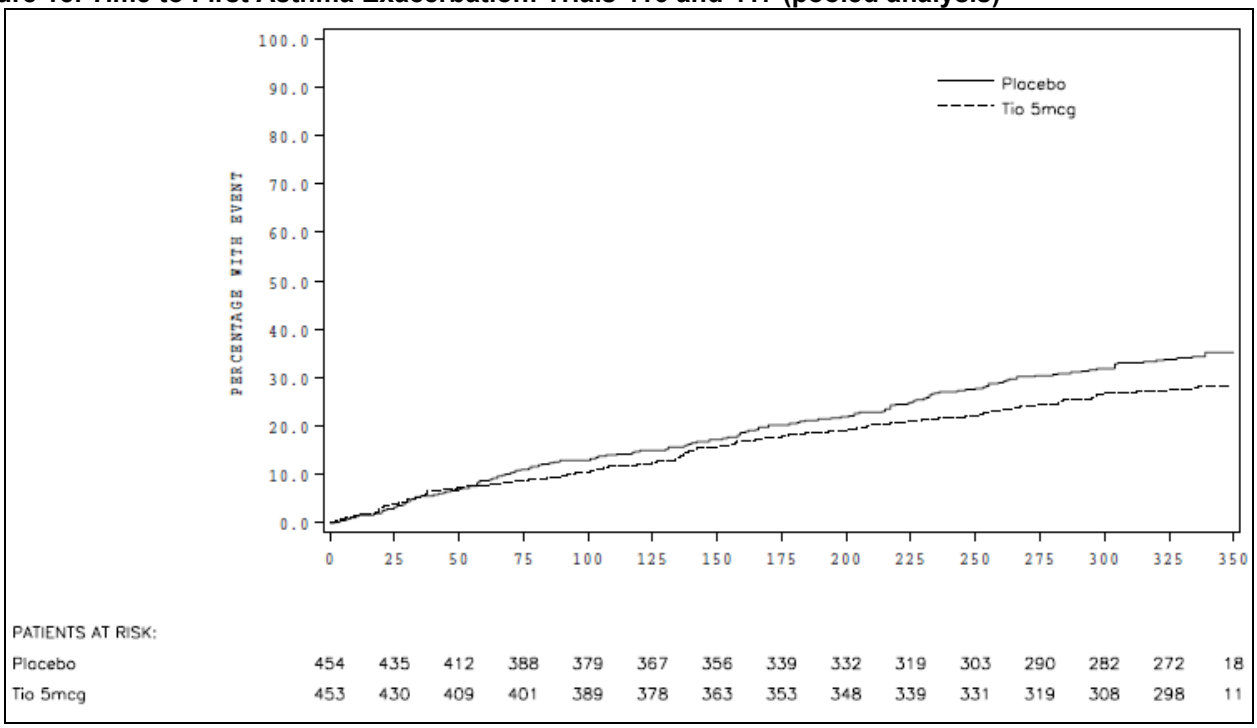
Although using a decrease in PEF to facilitate early assessment of exacerbations and response to treatment may be useful in practice, particularly for patients who are "poor perceivers" of airflow obstruction, asymptomatic decreases in PEF do not represent clinically meaningful asthma exacerbations in a drug development program. Because there is no standardized definition of a severe exacerbation, this review will refer to events meeting the aforementioned definition of any asthma exacerbation as "asthma worsening" and to the subset of exacerbations categorized as "severe" by the Applicant as "asthma exacerbations". Use of this terminology is intended to avoid confusion with the regulatory term "serious", which would indicate an event leading to hospitalization,

intubation, or death. Since asthma worsenings were not considered clinically relevant, the focus of this review will be on asthma exacerbations that required treatment with systemic corticosteroids. Furthermore, this review explores the data to determine if there is a differential treatment effect on asthma exacerbations that meet the regulatory definition for a serious adverse event.

Because the analyses of exacerbations were derived from pooled data rather than replicate trials, a reduction in exacerbations serves to support SR as a bronchodilator in asthma, (b) (4). Although all trials captured exacerbations as a secondary endpoint using the same definition, the frequency of exacerbation events in the 12-week trials was too low to draw any conclusions; therefore, only data from the 24 to 48-week trials are presented in this review.

Trials 416 and 417 were each 48 weeks in duration and enriched with patients who had experienced one or more asthma exacerbations in the past year. Time to first asthma exacerbation, defined as the time until at least 25% of patients had the event, from the pooled analysis is shown in the figure below.

Figure 15. Time to First Asthma Exacerbation: Trials 416 and 417 (pooled analysis)



Source: Study 205.416 and 205.417 Combined CSR, Figure 15.2.1.1.1:1

Once-daily treatment with SR 5 demonstrated a statistically significant improvement compared with placebo regarding time to first asthma exacerbation, which was 282 days and 226 days for SR 5 and placebo, respectively. The hazard ratio for SR 5 versus

placebo was 0.79 (95% CI 0.62, 1.00). This represents a 21% risk reduction for experiencing at least one asthma exacerbation for subjects treated with SR 5 compared with placebo (adjusted p-value=0.034).

Over the course of the 48-week trials, the majority of patients did not experience an asthma exacerbation. However, the number of patients with at least one asthma exacerbation was lower in the SR treatment group: 122 (27%) of SR-treated patients compared with 149 (33%) of placebo-treated patients. Using Fisher's exact test, this represents an odds ratio for SR 5 versus placebo of 0.75 (95% CI 0.56, 1.01). As shown in Table 31, the decrease in asthma exacerbations was primarily driven by the need for systemic corticosteroid treatment; however, there were nominally fewer asthma-related hospitalizations in the SR group. Additionally, three subjects (2 placebo, 1 SR 5) were hospitalized for asthma worsening (i.e., no systemic steroids received); these hospitalizations are not included in the table below. The Applicant did not specifically capture emergency room, urgent care, or unscheduled healthcare provider visits. Two subjects, both in the SR group, required intubation; however, there were no asthma-related deaths.

Table 31. Characterization of Asthma Exacerbations: Trials 416 and 417

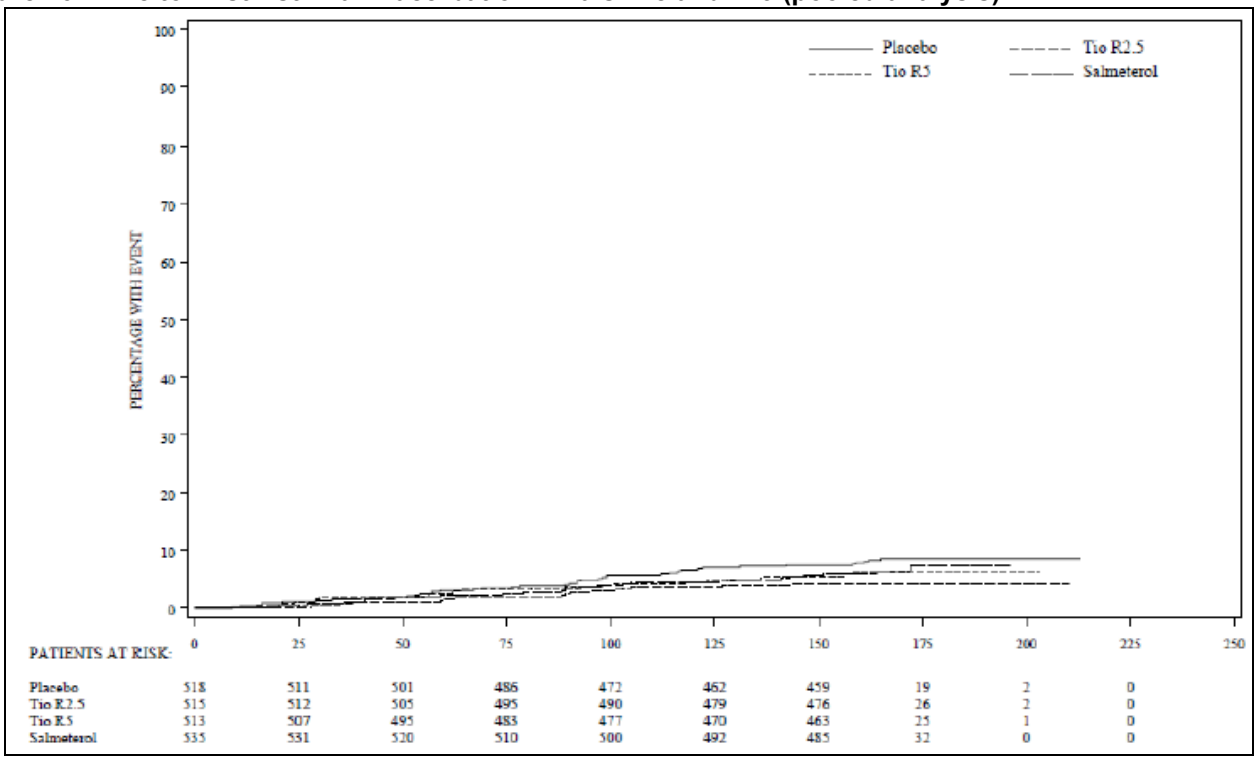
	416		417		416/417	
	SR 5 N=237	PBO N=222	SR 5 N=216	PBO N=232	SR 5 N=453	PBO N=454
Systemic steroids*	53 (22)	68 (31)	69 (32)	81 (35)	122 (27)	149 (33)
Initiation of systemic steroids	52	67	66	74	118	141
Doubling of current dose	4	5	4	10	8	15
Hospitalizations	8 (3)	9 (4)	7 (3)	9 (4)	15 (3)	18 (4)
Intubations	0	0	2 (1)	0	2 (0.4)	0
Deaths	0	0	0	0	0	0

N=number of subjects in Full Analysis Set
*Number of unique subjects treated with systemic corticosteroids for an asthma exacerbation. Subjects may have had more than one exacerbation treated with either initiation of systemic steroids or doubling of the current corticosteroid dose, and thus may be represented in both rows detailing the type of steroid received ("Initiation of systemic steroids" and "Doubling of current dose").
Source: Reviewer generated table in JReview using datasets POPU (POPUDC=FAS, POPUNY=1), GENTRT (TPATT), EXACERBS (PERIOD=1, EPTSEV=1, EPTCOR=1, or EPTDOU=1, or HOSP=1)

While trials 416 and 417 were the longest in duration and evaluated a clinically important event for difficult to control asthma, all subjects had fixed obstructive airway disease to the extent that would fulfill spirometric criteria for the diagnosis of COPD. Because SR 5 has already demonstrated efficacy for reducing exacerbations in COPD, the generalization of exacerbation data from these trials to broader asthma populations is limited. In addition, neither of these trials evaluated the 2.5 µg dose which consistently outperformed the 5 µg dose with regard to FEV_1 treatment effects. For these reasons, we examined exacerbation data captured as a secondary endpoint in trials 418, 419, and 444 which included both doses of SR. Note that trials 418 and 419 were 24 weeks in duration in adults with moderate asthma while trial 444 was 48 weeks in duration in adolescents with moderate asthma. All patients were uncontrolled on a

background therapy of medium-dose ICS. None of the trials were specifically enriched for patients with a history of frequent asthma exacerbations.

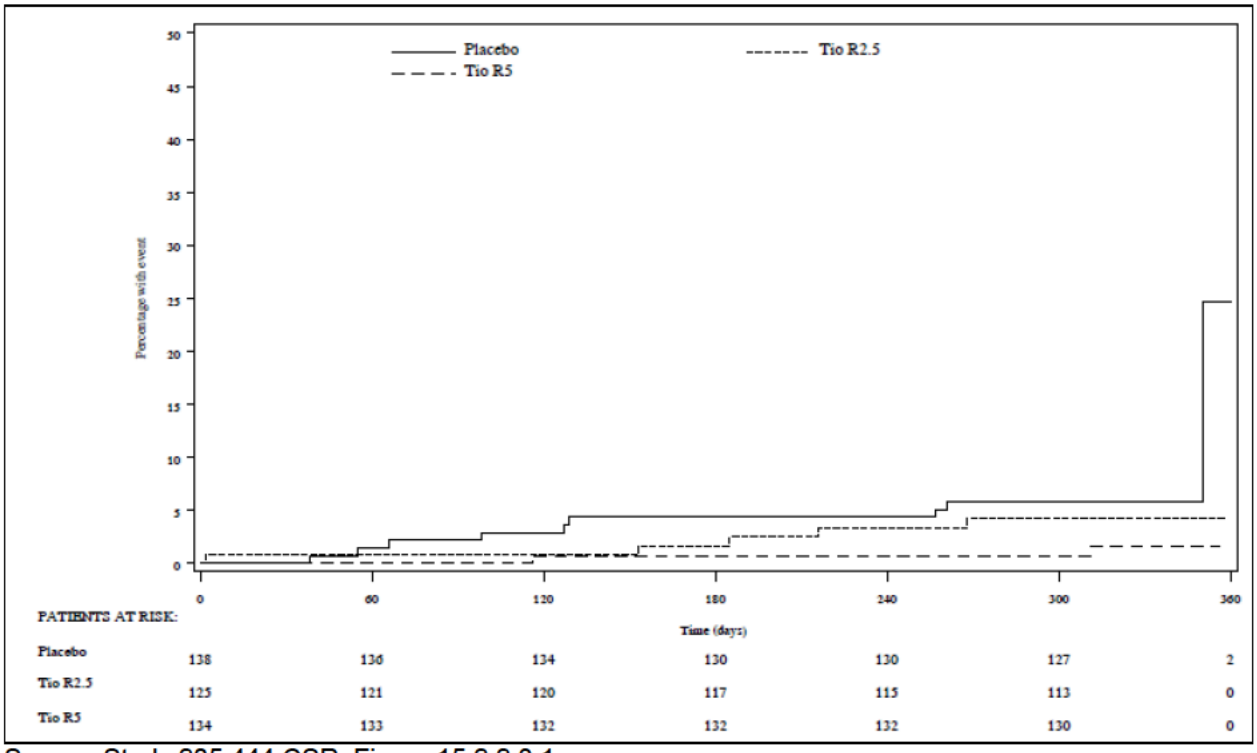
Figure 16. Time to First Asthma Exacerbation: Trials 418 and 419 (pooled analysis)



Source: Study 205.418 and 205.419 Combined CSR, Figure 11.4.1.2.1:1

In the pooled analysis of exacerbation data from trials 418 and 419, the risk of first asthma exacerbation was reduced in all active treatment arms compared to placebo with hazard ratios of 0.72, 0.50, and 0.75 for SR 5, SR 2.5, and salmeterol HFA groups, respectively. Although reported p-values are nominal because there were no pre-specified multiplicity corrections in place for secondary endpoints, only SR 2.5 resulted in a statistically significant reduction in asthma exacerbations over placebo (95% CI 0.30, 0.84). This represents a 50% reduction in the risk of experiencing an asthma exacerbation for subjects treated with SR 2.5 compared with placebo (p=0.008). These results suggest that there is no significant loss of efficacy between SR 5 and SR 2.5 with regard to reduction in exacerbations.

Figure 17. Time to First Asthma Exacerbation: Trial 444



Source: Study 205.444 CSR, Figure 15.2.2.3:1

In trial 444, the hazard ratio for the risk of first asthma exacerbation was 0.63 for SR 2.5 versus placebo and, 0.23 for SR 5 versus placebo. While both hazard ratios favored treatment with SR, neither were statistically significant (p=0.4 and 0.06, respectively).

The number of subjects reporting one or more asthma exacerbations in trials 418, 419, and 444 are shown in Table 32 below. In trials 418 and 419, fewer subjects in the SR 2.5 group experienced asthma exacerbations compared to subjects treated with either SR 5 or placebo; however, hospitalizations were rare in any group. Although subjects in trial 444 experienced the least number asthma exacerbations during treatment with SR 5, the number of exacerbations was relatively low and the single serious exacerbation resulting in hospitalization occurred in the SR 5 group. As before, the Applicant did not specifically capture emergency room, urgent care, or unscheduled healthcare provider visits in these trials. There were no asthma-related intubations or deaths reported.

Table 32. Characterization of Asthma Exacerbations: Trials 418, 419, and 444

	418			419			444		
	PBO N=265	SR 2.5 N=259	SR 5 N=261	PBO N=253	SR 2.5 N=256	SR 5 N=252	PBO N=138	SR 2.5 N=125	SR 5 N=134
Systemic steroids	24 (9)	9 (3)	17 (7)	19 (8)	13 (5)	14 (6)	9 (7)	5 (4)	2 (2)
Hospitalizations	1 (0.4)	0	0	1 (0.4)	1 (0.4)	0	0	0	1 (1)
Intubations	0	0	0	0	0	0	0	0	0

	418			419			444		
	PBO N=265	SR 2.5 N=259	SR 5 N=261	PBO N=253	SR 2.5 N=256	SR 5 N=252	PBO N=138	SR 2.5 N=125	SR 5 N=134
Deaths	0	0	0	0	0	0	0	0	0

N=Full Analysis Set
Source: Reviewer generated table in JReview using datasets POPU (POPUNY=1, POPU=FAS), GENTRT (TPATT), EXACIND (PERIODDC=Period 1, SEVFDC=Yes, and CORTICDC=Yes, or HOSPFDC=Yes)

Overall, treatment with SR reduces the risk of an asthma exacerbation that requires treatment with systemic corticosteroids. In trials 416 and 417 in subjects with fixed airway obstruction, there was also a numerical decrease in the number of asthma-related hospitalizations over a 48-week treatment period with the 5 µg dose. In trials which evaluated the 2.5 µg dose in a clear-cut asthma population, a similar benefit for reduced risk of asthma exacerbations was observed. Regarding asthma-related hospitalizations, there were too few to draw any conclusions regarding a beneficial effect on this outcome. Although the adolescent trials not powered to detect a statistically significant reduction in exacerbations, trends toward fewer exacerbations favored SR treatment groups.

6.1.6 Other Secondary Endpoints

The pre-specified primary endpoint for the pooled analysis of 418 and 419 was ACQ responder rate at 24 weeks, the results of which are displayed in Table 33. Notably, the responder rate was quite similar between the two SR doses, and thus provides further support for the effectiveness of SR 2.5 over placebo in the treatment of asthma.

Table 33. ACQ Responder Rate at 24 weeks: Trials 418 and 419 (pooled analysis)

	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 in the FAS population with measurements available at Week 24
Source: Statistical Review by Dr. Kiya Hamilton

Additional secondary endpoints analyzed by the Applicant are in Table 34 below; measurements shown are from the end of treatment for each trial as noted in the column headings. In general, the endpoints involving the change from baseline in Asthma Control Questionnaire (ACQ) score and peak expiratory flow (PEF) supported the primary and secondary endpoints by demonstrating a statistically significant benefit of SR over placebo. However, endpoints concerning the Asthma Quality of Life Questionnaire (AQLQ), nocturnal awakenings, rescue medication use, and number of

symptom-free days neither showed a significant difference from placebo nor demonstrated a consistent trend favoring any particular treatment group.

Table 34. Secondary Endpoints: Adult Trials

Difference from placebo	Trial 416 48 weeks	Trial 417 48 weeks	Trial 418 24 weeks	Trial 419 24 weeks	Trial 442 12 weeks
Mean AQLQ total score (units)					
SR 2.5	--	--	0.07 p=0.27	0.01 p=0.9	NA
SR 5	0.04 p=0.61	0.1 p=0.08	0.07 p=0.30	-0.003 p=0.96	NA
Salmeterol	--	--	0.20 p=0.002	0.08 p=0.21	--
Mean ACQ score (units)					
SR 2.5	--	--	-0.20 p<0.001	-0.13 p=0.03	0.06 p=0.36
SR 5	-0.1 p=0.07	-0.1 p=0.05	-0.11 p=0.03	-0.08 p=0.16	0.01 p=0.83
Salmeterol	--	--	-0.26 p<0.001	-0.12 p=0.03	--
Mean morning PEF (L/min)[1]					
SR 2.5	--	--	30.6 p<0.001	20.6 p<0.001	26.3 p<0.001
SR 5	20.3 p<0.001	14.0 p=0.002	23.7 p<0.001	24.8 p<0.001	25.6 p<0.001
Salmeterol	--	--	32.7 p<0.001	17.0 p<0.001	--
Mean evening PEF (L/min)[1]					
SR 2.5	--	--	28.2 p<0.001	16.0 p<0.001	22.4 p<0.001
SR 5	22.6 p<0.001	24.5 p<0.001	24.3 p<0.001	21.2 p<0.001	27.6 p<0.001
Salmeterol	--	--	28.9 p<0.001	11.7 p=0.01	--
Mean rescue medication use during 24 hr period (number of puffs)[1]					
SR 2.5	--	--	-0.2 p=0.24	-0.2 p=0.19	0.2 p=0.09
SR 5	-0.1 p=0.50	0.04 p=0.80	0.1 p=0.30	0.1 p=0.41	-0.03 p=0.80
Salmeterol	--	--	-0.5 p=0.001	-1.1 p=0.34	--
Mean number of nocturnal awakenings[1]					
SR 2.5	--	--	-0.02 p=0.53	0.01 p=0.85	0.01 p=0.86
SR 5	0.04 p=0.39	-0.001 p=0.99	-0.02 p=0.55	0.04 p=0.26	-0.04 p=0.31
Salmeterol	--	--	-0.07 p=0.03	-0.004 p=0.89	--
Mean number of symptom-free days[1,2]					
SR 2.5	--	--	0.05	-0.03	NA

Difference from placebo	Trial 416 48 weeks	Trial 417 48 weeks	Trial 418 24 weeks	Trial 419 24 weeks	Trial 442 12 weeks
			p=0.12	p=0.35	
SR 5	0.03 p=0.19	-0.01 p=0.64	-0.004 p=0.89	0.01 p=0.80	NA
Salmeterol	--	--	0.11 p<0.001	0.01 p=0.82	--

Abbreviations: AQLQ(S)=standardized asthma quality of life questionnaire, ACQ=asthma control questionnaire, PEF=peak expiratory flow, NA=Not analyzed
*All means adjusted for treatment, pooled center, visit/week, baseline, treatment by visit/week, baseline by visit/week
Results based on FAS population
[1]Weekly mean response at end of treatment period - defined as change of the mean of the last 7 days of treatment from study baseline weekly mean (defined as mean of last 7 days prior to Visit 2)
[2]Composite endpoint based on night-time awakenings, asthma symptoms during day, asthma symptoms during night, activity limitation, shortness of breath, wheezing and cough, daytime rescue medication use, and nighttime rescue medication use
Sources: CSR Tables 11.4.1.2.2:1, 15.2.1.5:1, 15.2.1.6:1, 15.2.1.6:2, 15.2.1.7.1:1, 15.2.1.7.1:2, 15.2.1.7.1:3, 15.2.1.7.2:1, 15.2.1.7.3.1:1, 15.2.1.7.3.3, 15.2.1.7.4:1, 15.2.1.7.10:1

Table 35. Secondary Endpoints: Adolescent Trials

Difference from placebo	Trial 444 48 weeks	Trial 456 12 weeks
Mean AQLQ(S)+12 total score (units)		
SR 2.5	0.14 p=0.11	NA
SR 5	0.03 p=0.72	NA
Mean ACQ score (units)		
SR 2.5	-0.19 p=0.03	0.06 p=0.48
SR 5	-0.13 p=0.14	0.04 p=0.66
Mean morning PEF (L/min)[1]		
SR 2.5	14.0 p=0.05	10.5 p=0.10
SR 5	19.6 p=0.01	17.4 p=0.01
Mean evening PEF (L/min)[1]		
SR 2.5	15.3 p=0.03	11.1 p=0.07
SR 5	18.2 p=0.01	17.6 p=0.004
Mean rescue medication use per day (number of puffs)[1]		
SR 2.5	-0.31 p=0.03	-0.001 p=1.0
SR 5	-0.28 p=0.05	-0.06 p=0.70
Mean number of nocturnal awakenings[1]		
SR 2.5	-0.04 p=0.42	0.09 p=0.04
SR 5	-0.05 p=0.24	0.05 p=0.27
Mean number of symptom-free days[1,2]		

Difference from placebo	Trial 444 48 weeks	Trial 456 12 weeks
SR 2.5	NA	0.002 p=0.95
SR 5	NA	-0.001 p=0.98

Abbreviations: AQLQ(S)+12=asthma quality of life questionnaire with standardized activities ≥12 years, ACQ=asthma control questionnaire, PEF=peak expiratory flow, NA=Not analyzed
*All means adjusted for treatment, country, week/visit, baseline, treatment by week/visit, baseline by week/visit. Results based on FAS population
[1]Weekly mean response at end of treatment period - defined as change of the mean of the last 7 days of treatment from study baseline weekly mean (defined as mean of last 7 days prior to Visit 2)
[2]Composite endpoint based on night-time awakenings, asthma symptoms during day, asthma symptoms during night, activity limitation, shortness of breath, wheezing and cough, daytime rescue medication use, and nighttime rescue medication use
Sources: CSR Tables 11.4.1.2.2:1, 15.2.2.2.1:1, 15.2.2.2.2:1, 15.2.2.4.1.1:1, 15.2.3.2.1:1, 15.2.3.2.1:2

6.1.7 Subpopulations

The Agency conducted subgroup analyses for FEV_1 $peak_{(0-3)}$ and trough FEV_1 by gender, race, and geographical region for the phase 3 efficacy trials. In general, these analyses revealed a favorable bronchodilator treatment effect with SR compared to placebo across various subgroups with no particular subgroup driving the results. However, it is important to note that the trials were not powered to detect differences based on subgroup analyses. Forest plots displaying subgroup analyses for each trial may be found in the Statistical Review by Dr. Kiya Hamilton.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Given that the lower 2.5 µg dose numerically outperformed the 5 µg dose as a bronchodilator and demonstrated similar reductions in asthma exacerbations in phase 3 trials, the Applicant was asked to provide further justification (b) (4) . In an amendment submitted on April 10, 2015, BI provided their dose justification which can be summarized as follows:

(b) (4)

(b) (4)

While the Applicant emphasized the importance of trough FEV_1 in their dose justification, the FEV_1 $peak_{(0-3)}$ is the more relevant FEV_1 measurement for a bronchodilator. Furthermore, FEV_1 $peak_{(0-3)}$ was the primary co-endpoint or primary endpoint in the phase 3 efficacy trials. Regarding efficacy in adolescents, the data were mixed with normal dose ordering observed in trial 444 and reverse dose ordering in trial 456; however, FEV_1 $peak_{(0-3)}$ was statistically significant for SR 2.5 in both trials. While it is true that the Applicant provided more data across varying asthma severities with SR 5, this ignores the fact that SR 2.5 was not evaluated in trials 416 and 417, which like many of the phase 3 trials were conducted prior to or concurrently with phase 2 dose-ranging studies. Therefore, the phase 2 study results must be interpreted within the context of the drug development timeline and integrated with the overall results from the larger and longer phase 3 trials which can also be considered dose-ranging in themselves as they evaluated both the 2.5 µg and 5 µg doses. Although trial 464 was primarily designed as a 52-week safety study, (b) (4) . The results for trough FEV_1 were statistically significant for SR 5, but not SR 2.5, at all time points, while FEV_1 $peak_{(0-3)}$ was not assessed. Although trough FEV_1 responses are inconsistent with those in the replicate 24-week trials 418 and 419, the primary objective of this trial was to evaluate safety, so any efficacy results are only supportive in nature and on their own cannot serve as the basis of approval or dose justification.

Acknowledging that there are no overt safety issues with the 5 µg dose (refer to Section 7 for a detailed safety review), an evaluation of the overall safety population revealed fewer asthma-related AEs reported during treatment with 2.5 µg dose compared with the 5 µg dose. Although this difference was not observed in subgroups of adolescent patients or mild asthmatics, the consistency of the efficacy results and trend toward fewer asthma-related AEs favoring the lower 2.5 µg, raises the question of whether or not the higher dose may have a subtle detrimental effect in asthma. (b) (4) .

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

As shown in Figure 14, time profile curves for FEV_1 $peak_{(0-3)}$ in weeks demonstrated a persistent bronchodilator effect for the duration of each trial. Similar findings were observed for trough FEV_1.

6.1.10 Additional Efficacy Issues/Analyses
None

7 Review of Safety

Safety Summary

This NDA submission contains adequate data to support the safety of Spiriva Respimat 2.5 µg (b) (4) once daily for the add-on maintenance treatment of asthma in patients 12 years of age and older. The evidence for safety in this population is based on seven 12 to 52-week trials in adults and two 12 to 48-week trials in adolescents, each in varying asthma severities.

In this safety review, adults and adolescents were evaluated separately, and there were no major safety concerns or new safety signals identified in either population. No deaths were reported in any of the trials, and asthma-related AEs, including serious, non-serious, and those leading to treatment withdrawal, generally occurred more frequently in the placebo groups. Regarding drug-class specific safety concerns, time-adjusted analyses revealed relatively low rates of systemic anticholinergic effects, such as dry mouth, with some evidence of a dose-dependent response between the 2.5 µg and 5 µg doses. Although cardiovascular safety was less of a concern following the completion and review of the TIOSPIR trial in COPD patients, the fact that very few MACE events occurred in the asthma trials with no apparent imbalance between treatment groups was nonetheless reassuring.

Finally, in regard to dose selection in asthma, there is no evidence in this safety database to suggest that the higher 5 µg dose is unsafe, a fact that is not unexpected given the experience with SR 5 in COPD, which could be considered a more fragile population. However, even when taking into account the asthma severity and treatment duration of the trials which evaluated both doses of SR versus SR5 only, there is a dose-dependent increase in some anticholinergic side effects, common AEs, and asthma-related AEs.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety
The primary safety database provided by the Applicant included all parallel group Phase 2 and 3 trials which are summarized with an enumeration of subjects in the following table. All trials were randomized, double-blind, placebo-controlled, and parallel group in design with a once daily dosing regimen for SR. Three of the trials (342, 442, and 464) were conducted entirely outside the U.S. Additionally, the study population in trial 342 consisted of patients who were homozygous for arginine at the 16th amino acid position of the β2-adrenergic receptor (B16-Arg/Arg). Although supporting safety data from Phase 2 crossover trials were also available, the data did not alter the overall safety

assessment and thus will not be discussed or included in this safety review. No secondary sources of data were utilized in the safety evaluation.

Table 36. Clinical Trials Used to Evaluate Safety

Trial	Treatment duration	Age (years)	Asthma severity	SR 2.5 (N=1039)	SR 5 (N=1634)	Salmeterol (N=675)	Placebo (N=1590)
Adults				**787**	**1370**	**675**	**1317**
Phase 2							
342†	16 weeks	18-65	Moderate	---	128	134	126
Phase 3							
416	48 weeks	18-75	Severe	---	237	---	222
417	48 weeks	18-75	Severe	---	219	---	234
418	24 weeks	18-75	Moderate	262	264	275	269
419	24 weeks	18-75	Moderate	257	253	266	254
442†	12 weeks	18-75	Mild	154	155	---	155
464†	52 weeks	18-75	Moderate-Severe	114	114	---	57
Adolescents				**252**	**264**	---	**273**
444	48 weeks	12-17	Moderate	125	134	---	138
456	12 weeks	12-17	Severe	127	130	---	135

N=Treated Set, defined as all randomized patients who took at least one dose of investigational treatment
†Trial conducted outside US
Source: Module 2.7.4, Summary of Clinical Safety, Table 1.1.1:1, p26

7.1.2 Categorization of Adverse Events

An adverse event (AE) was defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient or subject in a clinical investigation who was administered a pharmaceutical product; the event did not necessarily have a causal relationship with the treatment. AEs were recorded throughout the trials from screening at Visit 1 through 30 days after the last dose of trial medication and were followed until resolution or until follow-up was agreed in writing to be adequate by the monitor and investigator. A serious adverse event (SAE) was defined as any AE which resulted in death, was immediately life-threatening, resulted in persistent or significant disability/incapacity, required or prolonged patient hospitalization, was a congenital anomaly/birth defect, or was deemed serious due to any other medically important condition (i.e., if based upon appropriate medical judgment, it was an important medical event that may have jeopardized the patient, and may have required medical or surgical intervention to prevent one of the other above mentioned outcomes). Other significant AEs were defined as those non-serious, non-significant AEs that led to discontinuation or dose reduction of study medication. AEs were analyzed based on treatment-emergent adverse events (TEAEs), defined as all events with an onset any time following the first dose of study drug up to 30 days after the last administration of study drug.

Regarding categorization, AEs in the Summary of Clinical Safety (SCS) were coded using MedDRA version 16.1. In addition, the Applicant utilized standardized MedDRA queries (SMQs) and their own customized pharmacovigilance endpoints (PVs) to group multiple related MedDRA Preferred Terms (PTs) into clinically relevant categories. In general, the Applicant's coding of events from verbatim terms provided by investigators and subjects to PTs appears appropriate and consistent across trials and treatment groups.

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

The Applicant provided a number of safety analyses by employing a variety of pooling strategies according to SR dose, age, and asthma severity. Because adults and adolescents were evaluated in separate trials, this review analyzes the safety data separately as well. All parallel group trials in adults (342, 416, 417, 418, 419, 442, and 464) are pooled and presented together as the adult safety population. Pooled safety data in adolescents from trials 444 and 456 is presented separately in the pediatrics section of the review (Section 7.6.3). Time-adjusted rate analyses were used to explore the incidence of potential anticholinergic-related side effects and major adverse cardiovascular events (MACE) in the entire safety population.

7.2 Adequacy of Safety Assessments

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

The extent and duration of exposure in controlled clinical trials to both SR 2.5 µg and SR 5 µg adequately meets ICH guidelines for the safety evaluation of drugs intended for chronic use of a non-life-threatening disease. Although the Applicant evaluated adult and adolescent patients separately, this review considers both populations as contributing to the overall patient exposure since most asthma development programs combine all patients ≥ 12 years of age in phase 3 clinical trials.

Table 37. Extent of Exposure in Controlled Clinical Trials: Overall Safety Population

Extent of Exposure in Days, n (%)	SR 2.5 (N=1039)	SR 5 (N=1634)	Placebo (N=1590)
1-28	6 (1)	14 (1)	16 (1)
29-56	9 (1)	19 (1)	17 (1)
57-112	285 (28)	378 (23)	367 (23)
113-168	176 (17)	247 (15)	241 (15)
169-224	335 (32)	315 (19)	338 (21)
225-280	1 (<1)	7 (<1)	11 (<1)
281-336	47 (5)	192 (12)	191 (12)
337-363	73 (7)	343 (21)	342 (22)
≥365	107 (10)	119 (7)	67 (4)

N=Treated Set
Source: Module 5.3.5.3, SCS Supplement, Tables 1.1 and 1.2, p4373

Patient demographics in the safety population of adults (Table 38) and adolescents (Table 39) were relatively similar among treatment groups. In the adult safety population, there were slightly more females than males, while the adolescent safety population consisted primarily of males. Within the overall safety population, patients were predominantly White. Notably, there are relatively few Black/African American or Hispanic/Latino patients represented in the safety database.

Table 38. Demographic Profile of the Adult Safety Population

Demographic Parameters	SR 2.5 (N=787)	SR 5 (N=1370)	Salmeterol (N=675)	Placebo (N=1317)
Age (years)				
Mean (SD)	44 (13)	47 (13)	42 (13)	47 (14)
Range	18-74	18-75	18-74	18-75
Groups, n (%)				
<30 years	129 (16)	180 (13)	137 (20)	160 (12)
30-40 years	205 (26)	295 (22)	164 (24)	278 (21)
>40 years	453 (58)	895 (65)	374 (55)	879 (67)
Sex, n (%)				
Female	470 (60)	817 (60)	395 (59)	805 (61)
Race, n (%)				
White	374 (48)	857 (63)	391 (58)	864 (66)
Black	17 (2)	50 (4)	18 (3)	59 (5)
Asian	360 (46)	427 (31)	235 (35)	357 (27)
Hawaiian/Pacific Islander	2 (<1)	1 (<1)	0	2 (<1)
American Indian/Alaskan Native	34 (4)	35 (3)	31 (5)	35 (3)
Ethnicity*, n (%)				
Hispanic/Latino	71 (9)	83 (6)	58 (9)	80 (6)
Weight (kg)				
Mean (SD)	72 (19)	75 (18)	75 (19)	75 (19)
Range	37-163	35-160	32-181	31-180
Height (cm)				
Mean (SD)	165 (10)	166 (10)	167 (9)	166 (10)
Range	140-196	139 -198	142-196	139-198
BMI (kg/m^2)				
Mean (SD)	26 (6)	27 (6)	27 (6)	27 (6)
Range	15-65	15-63	11-60	14-62

Abbreviations: SR 2.5=Spiriva Respimat 2.5 µg/day, SR 5=Spiriva Respimat 5 µg/day, SD=standard deviation, BMI=body mass index
N=Treated Set from trials 342, 416, 417, 418, 419, 442, and 464
*Ethnicity missing for 342 (not collected in CRF)
Source: Module 5.3.5.3, SCS Supplement, Tables 4.1.1 and 4.1.2, p133

Table 39. Demographic Profile of the Adolescent Safety Population

Demographic Parameters	SR 2.5 (N=252)	SR 5 (N=264)	Placebo (N=273)	Total (N=789)
Age (years)				
Mean (SD)	14.3 (2)	14.4 (2)	14.2 (2)	14.3 (2)
Range	11-17	12-17	12-17	11-17
Groups				

Demographic Parameters	SR 2.5 (N=252)	SR 5 (N=264)	Placebo (N=273)	Total (N=789)
12-14 years	138 (55)	138 (52)	150 (55)	426 (54)
15-17 years	113 (45)	126 (48)	123 (45)	362 (46)
Sex, n (%)				
Female	91 (36)	92 (35)	106 (39)	289 (37)
Race, n (%)				
White	241 (96)	246 (93)	252 (92)	739 (94)
Black	7 (3)	6 (2)	9 (3)	22 (3)
Asian	4 (2)	10 (4)	9 (3)	23 (3)
Hawaiian/Pacific Islander	0	0	0	0
American Indian/Alaskan Native	0	2 (<1)	3 (1)	5 (<1)
Ethnicity, n (%)				
Hispanic/Latino	33 (13)	39 (15)	38 (14)	110 (14)
Weight (kg)				
Mean (SD)	59 (16)	60 (15)	56 (14)	58 (15)
Range	24-120	26-125	30-122	24-125
Height (cm)				
Mean (SD)	165 (11)	166 (12)	164 (11)	165 (11)
Range	136-195	132-196	138-190	132-196
BMI (kg/m^2)				
Mean (SD)	22 (5)	22 (4)	21 (4)	21 (4)
Range	13-43	14-40	14-38	13-43

Abbreviations: SR 2.5=Spiriva Respimat 2.5 µg/day, SR 5=Spiriva Respimat 5 µg/day, SD=standard deviation, BMI=body mass index
N=Treated Set from trials 444 and 456
Source, Module 5.3.5.3, SCS Supplement. Table 4.1.3, p139

7.2.2 Explorations for Dose Response

Since the 48-week adult trials (416 and 417) did not include the lower SR 2.5 µg dose, explorations for a dose response are primarily limited to trials of 24 weeks duration or less.

Table 40. Total Person Time Exposure in the Overall Safety Population

Exposure	Number of Patients	Patient Years
Adults and adolescents		
SR 2.5	1039	523
SR 5	1634	968
Placebo	1590	919
Adults		
SR 2.5	787	382
SR 5	1370	815
Adolescents	516	294
SR 2.5	252	141
SR 5	264	153

Exposure	Number of Patients	Patient Years
Adults by Asthma Severity		
Severe	456	398
Moderate	1036	468
Mild	309	71

Abbreviations: SR 2.5=Spiriva Respimat 2.5 µg/day, SR 5=Spiriva Respimat 5 µg/day
Source: Module 5.3.5.3, SCS Supplement, Tables 1.9 and 1.10, p4381 and Module 2.7.4 Summary of Clinical Safety, Table 1.2.2, p49

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was submitted or required.

7.2.4 Routine Clinical Testing

Routine testing included baseline clinical labs (CBC, serum chemistry), 12-lead ECG, and pregnancy testing at screening. The CBC included hemoglobin, hematocrit, erythrocyte count, leukocyte count and differential, total eosinophil count, and platelet count. The serum chemistry included lactate dehydrogenase, alanine transaminase, γ-glutamyl-transferase, aspartate transaminase, glucose, sodium, chloride, potassium, calcium, phosphate, creatinine, and total serum immunoglobulin E. Only trial 464 evaluated laboratory parameters beyond screening.

7.2.5 Metabolic, Clearance, and Interaction Workup

As previously mentioned in Section 4.4.3, the extent of metabolism is small as tiotropium bromide is mainly excreted unchanged in the urine. No dedicated drug-drug interaction studies were submitted to this NDA.

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

The adverse event datasets were analyzed to assess for adverse reactions associated with the anticholinergic pharmacologic action of tiotropium. Although cardiovascular safety was less of a concern following the completion of the TIOSPIR trial, the Applicant also analyzed adverse event datasets for MACE events and other cardiovascular PV and SMQ events, with the caveat that none of the trials were specifically designed to evaluate cardiovascular safety or mortality.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in this submission.

7.3.2 Nonfatal Serious Adverse Events

With the exception of asthma, the majority of nonfatal SAEs were single events without a clear relationship to treatment with SR. Overall, there were nominally fewer SAEs overall and SAEs due to asthma in the SR groups compared to placebo.

Table 41. Nonfatal SAEs in the Adult Safety Population

MedDRA SOC	MedDRA PT	Placebo N=1317	SR 2.5 N=787	SR 5 N=1370	Sal 50 N=675
Number of unique subjects with any SAE, n (%)		**65 (5)**	**16 (2)**	**55 (4)**	**18 (3)**
Cardiac disorders	Acute myocardial infarction	1 (0.1)	0	0	0
	Arrhythmia supraventricular	0	0	1 (0.1)	0
	Atrial fibrillation	0	1 (0.1)	1 (0.1)	0
	Coronary artery disease	1 (0.1)	0	0	0
	Coronary artery occlusion	0	0	1 (0.1)	0
	Coronary artery stenosis	0	0	1 (0.1)	0
	Myocardial infarction	0	1 (0.1)	0	0
	Ventricular tachycardia	0	0	1 (0.1)	0
Eye disorders	Cataract	1 (0.1)	0	0	0
	Vitreous hemorrhage	1 (0.1)	0	0	0
Gastrointestinal disorders	Abdominal discomfort	0	0	1 (0.1)	0
	Abdominal pain upper	1 (0.1)	0	0	0
	Anal fistula	0	1 (0.1)	0	0
	Colitis	0	0	1 (0.1)	0
	Diverticulum	1 (0.1)	0	0	0
	Duodenal obstruction	1 (0.1)	0	0	0
	Ileus paralytic	0	0	0	1 (0.1)
	Inguinal hernia	0	0	1 (0.1)	0
	Large intestine polyp	0	0	1 (0.1)	0
	Mechanical ileus	0	0	1 (0.1)	0
	Mesenteric hemorrhage	1 (0.1)	0	0	0
	Nausea	0	0	0	1 (0.1)
	Small intestinal obstruction	1 (0.1)	0	0	0
	Subileus	0	0	1 (0.1)	0
	Umbilical hernia	1 (0.1)	0	0	0
General disorders and administration site conditions	Adverse drug reaction	1 (0.1)	0	0	0
	Cyst	1 (0.1)	0	0	0
	Fat necrosis	0	0	1 (0.1)	0
	Suprapubic pain	0	1 (0.1)	0	0
Hepatobiliary disorders	Cholelithiasis	1 (0.1)	0	2 (0.1)	0
	Cirrhosis alcoholic	1 (0.1)	0	0	0
	Post cholecystectomy syndrome	1 (0.1)	0	0	0
Immune system disorders	Anaphylactic reaction	0	0	1 (0.1)	0
Infections and infestations	Abscess limb	0	0	1 (0.1)	0
	Appendicitis	1 (0.1)	0	0	0

MedDRA SOC	MedDRA PT	Placebo N=1317	SR 2.5 N=787	SR 5 N=1370	Sal 50 N=675
	Bronchopneumonia	0	0	1 (0.1)	0
	Cellulitis	1 (0.1)	1 (0.1)	1 (0.1)	0
	Chikungunya virus infection	1 (0.1)	0	0	0
	Cystitis	1 (0.1)	0	0	0
	Diverticulitis	1 (0.1)	0	0	0
	Enterocolitis infectious	1 (0.1)	0	0	0
	Gastroenteritis	0	1 (0.1)	0	2 (0.3)
	H1N1 influenza	1 (0.1)	0	0	0
	Influenza	0	1 (0.1)	0	0
	Lobar pneumonia	0	0	1 (0.1)	0
	Meningitis	0	0	1 (0.1)	0
	Peritonsillar abscess	1 (0.1)	0	0	0
	Pilonidal cyst	0	0	1 (0.1)	0
	Pneumonia	2 (0.2)	2 (0.3)	2 (0.1)	0
	Pneumonia bacterial	1 (0.1)	0	0	0
	Pyelonephritis	1 (0.1)	0	0	1 (0.1)
	Urinary tract infection	0	0	0	1 (0.1)
Injury, poisoning and procedural complications	Burns first degree	0	0	1 (0.1)	0
	Chemical poisoning	0	0	1 (0.1)	0
	Eye injury	0	0	1 (0.1)	0
	Fall	1 (0.1)	0	0	0
	Intestinal anastomosis complication	0	0	0	1 (0.1)
	Joint injury	0	0	0	1 (0.1)
	Ligament injury	0	0	0	1 (0.1)
	Post procedural bile leak	1 (0.1)	0	0	0
	Rib fracture	1 (0.1)	0	0	0
	Road traffic accident	1 (0.1)	0	0	0
	Sternal fracture	1 (0.1)	0	0	0
	Traumatic hematoma	1 (0.1)	0	0	0
Metabolism and nutrition disorders	Decreased appetite	1 (0.1)	0	0	0
	Dehydration	1 (0.1)	0	0	0
	Hypocalcaemia	1 (0.1)	0	0	0
	Hypoglycemia	0	0	1 (0.1)	0
	Hypokalemia	1 (0.1)	0	0	0
	Hyponatremia	1 (0.1)	0	0	0
Musculoskeletal and connective tissue disorders	Arthralgia	0	0	1 (0.1)	0
	Back disorder	0	0	1 (0.1)	0
	Back pain	1 (0.1)	0	0	0
	Bursitis	0	0	1 (0.1)	0
	Intervertebral disc protrusion	2 (0.2)	0	1 (0.1)	0
	Osteoarthritis	1 (0.1)	0	0	1 (0.1)
	Pain in extremity	0	1 (0.1)	0	0

MedDRA SOC	MedDRA PT	Placebo N=1317	SR 2.5 N=787	SR 5 N=1370	Sal 50 N=675
	Rhabdomyolysis	0	1 (0.1)	0	0
	Spinal osteoarthritis	1 (0.1)	0	0	0
	Vertebral foraminal stenosis	1 (0.1)	0	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Benign salivary gland neoplasm	0	0	1 (0.1)	0
	Bone cancer	1 (0.1)	0	0	0
	Gastrointestinal tract adenoma	1 (0.1)	0	0	0
	Intraductal proliferative breast lesion	0	0	1 (0.1)	0
	Invasive ductal breast carcinoma	0	0	1 (0.1)	0
	Ocular neoplasm	1 (0.1)	0	0	0
	Oral papilloma	0	1 (0.1)	0	0
	Ovarian adenoma	0	0	1 (0.1)	0
	Prostate cancer	0	0	1 (0.1)	0
	Small cell lung cancer	0	0	1 (0.1)	0
	Squamous cell carcinoma of skin	0	0	1 (0.1)	0
Nervous system disorders	Carpal tunnel syndrome	1 (0.1)	0	0	0
	Cerebral hemorrhage	1 (0.1)	0	0	0
	Cerebral infarction	0	0	1 (0.1)	0
	Cerebrovascular accident	2 (0.2)	0	1 (0.1)	1 (0.1)
	Cervical radiculopathy	0	1 (0.1)	0	0
	Facial paresis	1 (0.1)	0	0	0
	Headache	0	0	0	1 (0.1)
	Intracranial hematoma	0	0	0	1 (0.1)
	Loss of consciousness	1 (0.1)	0	0	0
	Paresthesia	0	0	1 (0.1)	0
Pregnancy, puerperium and perinatal conditions	Abortion spontaneous	1 (0.1)	0	0	0
	Abortion spontaneous complete	0	0	0	1 (0.1)
	Ectopic pregnancy	0	1 (0.1)	0	0
Psychiatric disorders	Major depression	0	0	1 (0.1)	0
	Mental status changes	0	0	1 (0.1)	0
Renal and urinary disorders	Renal failure	0	0	1 (0.1)	0
	Renal failure acute	1 (0.1)	0	0	0
Reproductive system and breast disorders	Benign prostatic hyperplasia	0	0	0	1 (0.1)
	Cervical dysplasia	0	0	1 (0.1)	0
	Ovarian cyst	0	0	1 (0.1)	0
	Parovarian cyst	0	0	1 (0.1)	0
Respiratory, thoracic and mediastinal disorders	Acute respiratory failure	0	0	1 (0.1)	0
	Asthma	27 (2)	2 (0.3)	19 (1)	6 (1)
	Dyspnea	0	0	1 (0.1)	0

MedDRA SOC	MedDRA PT	Placebo N=1317	SR 2.5 N=787	SR 5 N=1370	Sal 50 N=675
	Eosinophilic pneumonia	0	0	0	1 (0.1)
	Hemoptysis	0	1 (0.1)	0	0
	Hypoxia	0	0	1 (0.1)	0
	Nasal polyps	1 (0.1)	0	1 (0.1)	0
	Pneumothorax	0	0	1 (0.1)	0
	Pulmonary embolism	0	0	0	1 (0.1)
	Sinus polyp	0	0	1 (0.1)	0
	Sleep apnea syndrome	0	1 (0.1)	0	0
Surgical and medical procedures	Abortion induced	0	0	1 (0.1)	0
	Hip arthroplasty	0	0	1 (0.1)	0
Vascular disorders	Aortic dissection	1 (0.1)	0	0	0
	Deep vein thrombosis	1 (0.1)	0	0	1 (0.1)
	Hypertension	0	2 (0.3)	0	0
	Hypertensive crisis	0	0	1 (0.1)	0
	Hypotension	0	0	1 (0.1)	0
	Labile hypertension	1 (0.1)	0	0	0
	Shock	0	0	1 (0.1)	0

Abbreviations: SOC=System Organ Class, PT=Preferred Term, SR 2.5=tiotropium Respimat 2.5 µg/day, SR 5=tiotropium Respimat 5 µg/day, Sal 50=salmeterol HFA 50 µg twice daily,
N=Treated Set, n=number of subjects reporting the adverse event
Source: Reviewer generated table in JReview using datasets POPU (POPUDC=Treated set, POPUX does not equal "not treated", STUDY IN="205_342", "205_416", "205_417", "205_418", "205_419", "205_442", "205_464"), AEAN1001 (AESERA=1, CONDLVL=Preferred Term, ATONSLBL="MissTrtOnset", "Placebo", Postdb", "Post-study", "Post-treat", "Salmeterol", "Tio R2.5", or "Tio R5")

7.3.3 Dropouts and/or Discontinuations

Table 42 below displays the overall profile of dropouts from controlled, parallel group trials in adults as provided by the Applicant. Considering that SR 2.5 was not evaluated in trials 416 and 417, the number of premature treatment discontinuations overall and within each sub-category were similar. An analysis of the patient dropouts confirmed that the reason for discontinuation provided was generally appropriate; however, this reviewer identified a few cases from trials 416 and 417 that could reasonably have been categorized as adverse dropouts due to worsening of asthma rather than "other" or "lack of efficacy". These cases are identified in Table 43, but do not significantly alter the safety assessment that relatively few patients discontinued treatment due to an adverse event or experience. The majority of adverse dropouts were due to asthma with a greater number originating from the placebo treatment group.

Table 42. Dropout Profile: Incidence of Dropouts by Treatment Group and Reason in the Adult Safety Population

Reason for dropout	Placebo N=1317	SR 2.5 N=787	SR 5 N=1370	Salmeterol N=675
Prematurely discontinued	99 (7.5)	38 (4.8)	102 (7.4)	38 (5.6)
Adverse Event	30 (2.3)	9 (1.1)	26 (1.9)	12 (1.8)
Worsening of asthma	16 (1.2)	4 (0.5)	9 (0.7)	5 (0.7)

Reason for dropout	Placebo N=1317	SR 2.5 N=787	SR 5 N=1370	Salmeterol N=675
Worsening of other pre-existing disease	1 (0.1)	1 (0.1)	2 (0.1)	2 (0.3)
Other AE	13 (1.0)	4 (0.5)	15 (1.1)	5 (0.7)
Lack of efficacy	3 (0.2)	0	3 (0.2)	0
Noncompliant with protocol	10 (0.8)	6 (0.8)	10 (0.7)	2 (0.3)
Lost to follow-up	8 (0.6)	2 (0.3)	5 (0.4)	5 (0.7)
Consent withdrawn not due to AE	23 (1.7)	6 (0.8)	22 (1.6)	6 (0.9)
Other	25 (1.9)	15 (1.9)	36 (2.6)	13 (1.9)

Includes trials 342, 416, 417, 418, 419, 442, 464
N=Treated Set
Source: SCS Supplement, Appendix 1, Tables 2.3, 2.4, and 2.7, p112, 113, and 116

Table 43. Adverse Dropouts by Subject: Adult Safety Population

Subject ID	Age/ Sex	Race	Onset (study day)	Preferred Term	SAE	Maximum intensity	Therapy required	Outcome
SR 2.5								
418 1597	32/F	W	16	Extrasystoles	N	moderate	Y	resolved
418 1665	64/F	W	117	Atrial fibrillation	Y	severe	Y	resolved
418 4271	37/F	A	131	Gastroesophageal reflux disease	N	severe	Y	resolved
418 5244	64/M	W	116	Hemoptysis	Y	moderate	Y	resolved
			116	Myocardial infarction	Y	moderate	Y	resolved
419 1127	33/M	W	2	Asthma	N	severe	Y	resolved
419 1668	50/M	W	99	Oropharyngeal pain	N	moderate	N	resolved
442 0755	65/F	W	50	Asthma	N	severe	Y	resolved
442 0757	25/M	W	29	Asthma	N	mild	Y	resolved
464 0103	64/F	A	141	Asthma	N	moderate	Y	resolved
SR 5								
342 0401	33/F	W	56	Bronchitis	N	severe	Y	resolved
342 0516	47/M	W	2	Sleep disorder	N	moderate	N	resolved
342 1016	35/M	W	33	Hypertension	N	moderate	N	resolved
342 1222	55/F	W	50	Asthma	N	moderate	Y	resolved
342 1437	30/M	W	66	Asthma	N	moderate	Y	resolved
416 0006	70/M	W	95	Cerebrovascular accident	Y	severe	Y	resolved with sequelae
416 0402	66/F	W	185	Bronchiectasis	N	moderate	N	not resolved
416 1807	66/F	W	175	Arthritis	N	moderate	N	not resolved
416 1808	49/F	W	192	Asthma	Y	severe	Y	resolved
416 2770	62/F	W	84	Asthma	Y	moderate	Y	resolved
416 3650	61/M	A	4	Erythema	N	mild	N	recovered
417 0207	42/F	B	179*	Consent withdrawn/other[1]	N	severe	Y	resolved
417 0807	40/F	W, H	36	Dysphonia	N	moderate	N	resolved
			55	Muscle spasms	N	moderate	N	resolved
417 0863	68/F	W, H	167*	Lack of efficacy/other[2]	N	severe	Y	resolved

Subject ID	Age/ Sex	Race	Onset (study day)	Preferred Term	SAE	Maximum intensity	Therapy required	Outcome
417 2687	48/F	W	52	Asthma	N	severe	Y	resolved
418 1073	63/F	W	72	Asthma	N	moderate	Y	resolved
			72	Sinusitis	N	moderate	Y	resolved
418 1166	52/M	B	-16	Dyspnea	N	moderate	Y	resolved
418 1342	62/F	W	169	Electrocardiogram ST segment depression	N	moderate	N	resolved
418 1400	44/F	W,H	175	Asthma	N	mild	Y	resolved
418 1662	46/F	B	113	Vision blurred	N	mild	N	resolved
			127	Non-cardiac chest pain	N	moderate	Y	resolved
418 2709	34/F	A	59	Dysphonia	N	moderate	N	resolved
418 4107	22/M	A	87	Urticaria	N	moderate	N	resolved
418 7388	43/F	W	20	Asthma	N	moderate	Y	resolved
			8	Dry throat	N	moderate	N	resolved
			14	Pharyngeal hypoesthesia	N	moderate	Y	resolved
419 1474	59/F	W	109	Colitis	Y	severe	Y	resolved
419 2054	26/M	A	2	Drug hypersensitivity	N	mild	Y	resolved
442 0934	50/F	W	7	Intraductal proliferative breast lesion	Y	severe	Y	resolved
464 2205	71/M	A	154	Asthma, bronchitis	N	moderate	Y	resolved
464 4705	63/F	A	25	Atrioventricular block first degree, supraventricular extrasystoles, ventricular extrasystoles. hypertension, palpitations	N	mild	Y	resolved

*Study Day disposition term reported
[1] Patient withdrew due to repeated asthma exacerbations
[2] Reason for discontinuation: high use of rescue meds, low FEV_1, and too many exacerbations
Source: Reviewer generated table in JReview using datasets POPU (POPUDC=Treated set, POPUX does not equal "not treated", STUDY IN="205_342", "205_416", "205_417", "205_418", "205_419", "205_442", "205_464"), DS (EPOCH="treatment period"), AEAN1001 (CONDLVL=Preferred Term, ATONSLBL="Tio R2.5", or "Tio R5", AEACTA=3)

In subjects treated with placebo, adverse dropouts were reported for the following reasons (each PT indicates one subject unless otherwise indicated in parentheses):

- 342 – lichenoid keratosis, chest discomfort
- 416 – asthma (4), urinary incontinence, headache, throat irritation
- 417 – asthma (4), bronchospasm, headache, bone neoplasm malignant, road traffic accident
- 418 – asthma (4), acute myocardial infarction/coronary artery disease, ventricular extrasystoles, spontaneous abortion, gastrointestinal tract adenoma

- 419 – asthma (3), dyspnea/tremor, cerebral hemorrhage
- 464 – aortic dissection

In subjects treated with salmeterol, adverse dropouts were reported for the following reasons:

- 342 – asthma, chest pain
- 418 – rash, asthma, hernia
- 419 – asthma (3), eosinophilic pneumonia, viral upper respiratory tract infection, tachycardia, pruritus

7.3.4 Significant Adverse Events

This section includes an analysis of severe adverse events. The overall rate of severe AEs was similar between active and placebo treatment groups, and for the most part severe AEs occurred as single events. The table below displays all severe AEs occurring at greater frequency than placebo in the adult safety population; AEs which also met the regulatory definition of an SAE or led to treatment discontinuation are noted. The most commonly reported severe AE was asthma, which occurred at a slightly greater frequency in the placebo group (and thus is not shown). Although fewer subjects received SR 2.5, the overall percentage of subjects experiencing severe TEAEs was lower in the SR 2.5 treatment group.

Table 44. Severe TEAEs (occurring at a greater frequency than placebo): Adult Safety Population

MedDRA SOC/PT	Placebo N=1317	SR 2.5 N=787	SR 5 N=1370	Sal 50 N=675
Number of subjects with severe TEAEs	**77 (6)**	**17 (2)**	**94 (7)**	**27 (4)**
Cardiac disorders				
Arrhythmia supraventricular	0	0	1 (0.1)*	0
Atrial fibrillation	0	1 (0.1)*†	1 (0.1)*	0
Sinus tachycardia	0	0	1 (0.1)	0
Ventricular tachycardia	0	0	1 (0.1)*	0
Gastrointestinal disorders				
Abdominal distension	0	0	1 (0.1)	0
Abdominal hernia	0	0	1 (0.1)	0
Anal fistula	0	1 (0.1)*	0	0
Colitis	0	0	1 (0.1)*†	0
Diarrhea	1 (0.1)	0	5 (0.4)	0
Dry mouth	0	1 (0.1)	0	0
Dyspepsia	0	0	1 (0.1)	0
Enteritis	0	0	1 (0.1)	0
Food poisoning	0	0	1 (0.1)	0
Gastritis	0	0	1 (0.1)	0
Gastritis erosive	0	1 (0.1)	0	0
Gastroesophageal reflux disease	0	1 (0.1)†	1 (0.1)	0

MedDRA SOC/PT	Placebo N=1317	SR 2.5 N=787	SR 5 N=1370	Sal 50 N=675
Ileus paralytic	0	0	0	1 (0.1)*
Mechanical ileus	0	0	1 (0.1)*	0
Periodontal disease	0	1 (0.1)	0	0
General disorders and administration site conditions				
Asthenia	0	0	1 (0.1)	0
Face edema	0	0	1 (0.1)	0
Suprapubic pain	0	1 (0.1)*	0	0
Thirst	0	0	1 (0.1)	0
Hepatobiliary disorders				
Cholelithiasis	0	0	1 (0.1)*	0
Immune system disorders				
Anaphylactic reaction	0	0	1 (0.1)*	0
Infections and infestations				
Acute sinusitis	0	0	1 (0.1)	0
Bronchitis, bronchitis viral	1 (0.1)	0	1 (0.1)†	1 (0.1)
Cellulitis	0	1 (0.1)*	0	0
Gastroenteritis	0	1 (0.1)*	0	2 (0.3)*
H1N1 influenza, influenza	2 (0.2)*	0	2 (0.1)	0
Osteomyelitis	0	0	1 (0.1)	0
Otitis media acute	0	0	1 (0.1)	0
Pertussis	0	0	1 (0.1)	0
Pharyngitis	1 (0.1)	0	1 (0.1)	0
Pneumonia, lobar pneumonia	2 (0.2)*	0	4 (0.3)*	0
Rhinitis	0	0	1 (0.1)	0
Tooth abscess	1 (0.1)	0	0	1 (0.1)
Tooth infection	0	0	1 (0.1)	0
Injury, poisoning and procedural complications				
Burns first degree	0	0	1 (0.1)*	0
Chemical poisoning	0	0	1 (0.1)*	0
Contusion	0	1 (0.1)	0	0
Eye injury	0	0	1 (0.1)*	0
Hand fracture	0	0	1 (0.1)	0
Intestinal anastomosis complication	0	0	0	1 (0.1)*
Ligament injury	0	0	0	1 (0.1)*
Post-traumatic pain	0	0	1 (0.1)	0
Rib fracture	0	0	1 (0.1)	0
Road traffic accident	1 (0.1) *†	0	1 (0.1)	0
Tendon injury	0	1 (0.1)	0	0
Tendon rupture	0	0	1 (0.1)	0
Upper limb fracture	0	0	1 (0.1)	0
Investigations				
Biopsy breast	0	0	1 (0.1)	0
Metabolism and nutrition disorders				

MedDRA SOC/PT	Placebo N=1317	SR 2.5 N=787	SR 5 N=1370	Sal 50 N=675
Hypoglycemia	0	0	1 (0.1)*	0
Type 1 diabetes mellitus	0	0	0	1 (0.1)
Musculoskeletal and connective tissue disorders				
Arthralgia	1 (0.1)	0	1 (0.1)	0
Arthritis	0	0	1 (0.1)	0
Bursitis	0	0	1 (0.1)*	0
Intervertebral disc disorder	0	0	1 (0.1)	0
Muscle spasms	0	0	2 (0.1)	0
Musculoskeletal pain	0	0	1 (0.1)	0
Neck pain	0	0	1 (0.1)	0
Rhabdomyolysis	0	1 (0.1)*	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)				
Intraductal proliferative breast lesion	0	0	1 (0.1)*†	0
Invasive ductal breast carcinoma	0	0	1 (0.1)*	0
Ovarian adenoma	0	0	1 (0.1)*	0
Prostate cancer	0	0	1 (0.1)*	0
Small cell lung cancer	0	0	1 (0.1)*	0
Uterine leiomyoma	0	0	1 (0.1)	0
Nervous system disorders				
Cerebral infarction	0	0	1 (0.1)*	0
Cerebrovascular accident	0	0	1 (0.1)*†	1 (0.1)*
Dizziness	0	0	1 (0.1)	0
Headache	2 (0.2)	0	2 (0.1)	1 (0.1)*
Intracranial hematoma	0	0	0	1 (0.1)*
Migraine	0	0	1 (0.1)	2 (0.3)
Paresthesia	0	0	1 (0.1)*	0
Sciatica	1 (0.1)	0	1 (0.1)	0
Pregnancy, puerperium and perinatal conditions				
Abortion spontaneous	1 (0.1)*†	0	0	1 (0.1)*
Psychiatric disorders				
Major depression	0	0	1 (0.1)*	0
Mental status changes	0	0	1 (0.1)*	0
Stress	0	0	1 (0.1)	0
Renal and urinary disorders				
Nephrolithiasis	0	0	1 (0.1)	0
Renal failure, renal failure acute	1 (0.1)*	0	1 (0.1)*	0
Reproductive system and breast disorders				
Benign prostatic hyperplasia	0	0	0	1 (0.1)*
Breast mass	0	0	1 (0.1)	0
Cervical dysplasia	0	0	1 (0.1)*	0
Parovarian cyst	0	0	1 (0.1)*	0
Respiratory, thoracic and mediastinal disorders				
Acute respiratory failure	0	0	1 (0.1)*	0

MedDRA SOC/PT	Placebo N=1317	SR 2.5 N=787	SR 5 N=1370	Sal 50 N=675
Cough	0	0	0	1 (0.1)
Dyspnea	1 (0.1)	0	1 (0.1)*	0
Eosinophilic pneumonia	0	0	0	1 (0.1) *†
Hypoxia	0	0	1 (0.1)*	0
Nasal obstruction	0	1 (0.1)	0	0
Oropharyngeal pain	0	0	1 (0.1)	0
Pneumothorax	0	0	1 (0.1)*	0
Skin and subcutaneous tissue disorders				
Eczema	0	0	1 (0.1)	1 (0.1)
Urticaria	0	0	0	1 (0.1)
Surgical and medical procedures				
Abortion induced	0	0	1 (0.1)*	0
Vascular disorders				
Hypertension	1 (0.1)	1 (0.1)*	1 (0.1)	0
Hypotension	0	0	1 (0.1)*	0
Shock	0	0	1 (0.1)*	0

*At least one event met the regulatory definition of a serious adverse event
†At least one event led to withdrawal of treatment
Source: Reviewer generated table in JReview using datasets POPU (POPUDC=Treated set, POPUX does not equal "not treated", STUDY IN="205_342", "205_416", "205_417", "205_418", "205_419", "205_442", "205_464"), AEAN1001 (CONDLVL=Preferred Term, ATONSLBL="MissTrtOnset", "Placebo", Postdb", "Post-study", "Post-treat", "Salmeterol", "Tio R2.5", or "Tio R5", AEINT=3, AEONDTTM ≥1)

7.3.5 Submission Specific Primary Safety Concerns

Given the well-known side effects of anticholinergic agents, this review collected and analyzed AEs that could have potentially been caused by the pharmacologic action of tiotropium such as dry mouth (dental caries, gum/buccal mucosal ulceration), decreased bronchial secretions (mucus plugging), decreased sweating (hyperthermia, flushing, fever), increased pupil size (photophobia, acute narrow angle glaucoma), blurry vision, increased heart rate (angina, MI), urinary retention, decreased GI motility (constipation), impaired concentration, confusion, attention deficit, memory impairment, drowsiness, or sedation. To aid in the detection of these potential anticholinergic AEs, the table below displays a time-adjusted rate difference between placebo and SR treatments for the adult safety population. The time at risk was approximately 860 patients-years for placebo, 446 patient-years for SR 2.5 µg , and 917 patient-years for SR 5 µg .

Overall, it appears that the frequency of potential anticholinergic side effects was relatively low overall, although some AEs such as dry mouth occurred twice as frequently with the higher 5 µg dose. Adverse reactions more common in the older COPD population for whom SR is currently approved, such as urinary retention, were not reported in the asthma clinical trials. Although decreased bronchial secretions leading to mucus plugging could have been an adverse reaction unique to the asthma population, there was no apparent evidence of this based on a review of the AE listings

and datasets. In addition, asthma was reported as an AE/SAE more frequently by placebo-treated patients.

Table 45. Potential Drug Class-related Adverse Events in the Adult Safety Population

Preferred Term	Placebo N=1317		SR 2.5 N=787		SR 5 N=1370	
	n (%) with event	Rate/100 patient-years	n (%) with event	Rate/100 patient-years	n (%) with event	Rate/100 patient-years
Arrhythmia	0	0	0	0	1 (0.1)	0.1
Arrhythmia supraventricular	0	0	0	0	1 (0.1)	0.1
Atrial tachycardia	0	0	0	0	1 (0.1)	0.1
Palpitations	5 (0.4)	0.6	4 (0.5)	0.9	7 (0.5)	0.8
Sinus arrhythmia	1 (0.1)	0.1	0	0	0	0
Sinus tachycardia	1 (0.1)	0.1	1 (0.1)	0.2	2 (0.1)	0.2
Tachycardia	6 (0.5)	0.7	0	0	2 (0.1)	0.2
Ventricular tachycardia	0	0	1 (0.1)	0.2	1 (0.1)	0.1
Dry eye	1 (0.1)	0.1	1 (0.1)	0.2	2 (0.1)	0.2
Vision blurred	1 (0.1)	0.1	0	0	3 (0.2)	0.3
Intraocular pressure increased	1 (0.1)	0.1	0	0	0	0
Dry mouth	7 (0.4)	0.7	3 (0.4)	0.7	14 (0.9)	1.3
Dry throat	1 (0.2)	0.1	1 (0.1)	0.2	6 (0.4)	0.6
Lip dry	0	0	0	0	1 (0.1)	0.1
Thirst	3 (0.2)	0.3	3 (0.4)	0.7	10 (0.7)	1.1
Polydipsia	0	0	1 (0.1)	0.2	0	0
Dental caries	4 (0.3)	0.5	2 (0.3)	0.4	4 (0.3)	0.4
Periodontal disease	0	0	1 (0.1)	0.2	1 (0.1)	0.1
Periodontitis	1 (0.1)	0.1	2 (0.2)	0.3	2 (0.1)	0.2
Gingivitis	0	0	2 (0.3)	0.4	2 (0.1)	0.2
Gingival ulceration	1 (0.1)	0.1	0	0	0	0
Mouth ulceration	1 (0.1)	0.1	0	0	0	0
Salivary duct obstruction	0	0	0	0	1 (0.1)	0.1
Constipation	8 (0.6)	0.9	1 (0.1)	0.2	4 (0.3)	0.4
Gastrointestinal motility disorder	1 (0.1)	0.1	0	0	0	0
Subileus	0	0	0	0	1 (0.1)	0.1
Feeling hot	0	0	0	0	1 (0.1)	0.1
Pyrexia	9 (0.7)	1.0	8 (1)	1.8	10 (0.7)	1.1
Dizziness	7 (0.5)	0.8	5 (0.6)	1.1	13 (0.9)	1.4
Memory impairment	1 (0.1)	0.1	0	0	0	0
Somnolence	3 (0.2)	0.3	1 (0.1)	0.2	0	0

Includes trials 432, 416, 417, 418, 419, 442, 464
Source: Module 5.3.5.3, SCS Supplement, Appendix 2, Tables 2.10.1.5 and 2.10.1.7

Following the review and public discussion of the TIOSPIR trial in COPD patients, cardiovascular safety of SR was less of a concern with this submission. However, the Applicant provided a time-adjusted analysis of MACE events in the overall safety population (adults and adolescents) which are shown in the table below. Because there were no deaths in the asthma development program, fatal MACE events have been omitted. Even though none of the trials were specifically designed to evaluate

cardiovascular morbidity and mortality, events occurred at a very low rate in this younger patient population, and there was no significant difference between active and placebo treatment.

Table 46. Time-adjusted Rate Difference of MACE Endpoints in the Overall Safety Population

Time at Risk (patient – years)	Placebo N=1590		SR 2.5 N=1039		SR 5 N=1634	
	1040.1		608.1		1091.8	
MACE Event*	n(%) with event	Rate/100 pt-years	n(%) with event	Rate/100 pt-years	n(%) with event	Rate/100 pt-years
Sub-SMQ Myocardial infarction (broad)	1 (0.1)	0.1	1 (0.1)	0.2	2 (0.1)	0.2
Stroke (any)	3 (0.2)	0.3	0	0	2 (0.1)	0.2

*Fatal MACE events not listed
Source: Module 5.3.5.4, SCS supplement, Appendix 2 Tables 2.11.5 and 2.11.6, p7064-7067

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Treatment-emergent events occurring with a frequency of at least 1% in either SR treatment group and with a greater frequency than placebo are shown in the following table. Some side effects such as dry mouth or throat are expected, while others such as GERD and bronchitis are not currently listed in the product label. Notably, the placebo group experienced numerically more AEs of asthma, decreased PEF, wheezing, coughing, dyspnea, hypoxia, and bronchospasm than the tiotropium group; this trend is consistent with the lower number of significant asthma-related AEs (SAEs, severe AEs, and treatment discontinuations) observed in the SR groups.

Table 47. Common TEAEs occurring ≥ 1% in SR groups (and greater than placebo): Adult Safety Population

MedDRA SOC and PT	Placebo N=1317	SR 2.5 N=787	SR 5 N=1370	Salmeterol N=675
	823 (63)	449 (57)	833 (61)	350 (52)
Gastrointestinal disorders				
Abdominal pain, abdominal pain upper, abdominal discomfort[1]	10 (0.8)	12 (1.5)	22 (1.6)	2 (0.3)
Diarrhea	11 (0.8)	8 (1.0)	16 (1.2)	6 (0.9)
Dry mouth	7 (0.5)	3 (0.4)	14 (1.0)	2 (0.3)
Gastroesophageal reflux disease, gastritis, dyspepsia, gastritis erosive[1]	23 (1.7)	14 (1.8)	36 (2.6)	4 (0.6)
General disorders and administration site conditions				
Pyrexia	9 (0.7)	8 (1.0)	9 (0.7)	1 (0.1)
Infections and infestations				
Bronchitis, bronchitis viral, bronchitis bacterial[1]	31 (2.4)	25 (3.2)	56 (4.1)	16 (2.4)

MedDRA SOC and PT	Placebo N=1317	SR 2.5 N=787	SR 5 N=1370	Salmeterol N=675
Gastroenteritis, gastroenteritis viral, gastroenteritis bacterial[1]	13 (1.0)	8 (1.0)	31 (2.3)	5 (0.7)
Influenza, H1N1 influenza[1]	30 (2.3)	8 (1.0)	35 (2.6)	4 (0.6)
Nasopharyngitis	142 (10.8)	102 (13.0)	153 (11.2)	44 (6.5)
Oral candidiasis, oral fungal infection[1]	8 (0.6)	6 (0.8)	18 (1.3)	1 (0.1)
Pharyngitis	17 (1.3)	26 (3.3)	28 (2.0)	7 (1.0)
Respiratory, thoracic and mediastinal disorders				
Dysphonia	11 (0.8)	4 (0.5)	26 (1.9)	1 (0.1)
Oropharyngeal pain or discomfort[1]	18 (1.4)	17 (2.2)	28 (2.0)	4 (0.6)
Seasonal allergy, rhinitis allergic, rhinitis perennial, rhinitis seasonal[1]	19 (1.4)	19 (2.4)	31 (2.3)	12 (1.8)
Vascular disorders				
Hypertension	16 (1.2)	13 (1.7)	19 (1.4)	8 (1.2)

[1]Similar preferred terms combined
Source: Reviewer generated table in JReview using datasets POPU (POPUDC=Treated set, POPUX does not equal "not treated", STUDY IN="205_342", "205_416", "205_417", "205_418", "205_419", "205_442", "205_464"), AEAN1001 (CONDLVL=Preferred Term, ATONSLBL="MissTrtOnset", "Placebo", Postdb", "Post-study", "Post-treat", "Salmeterol", "Tio R2.5", or "Tio R5"

7.4.2 Laboratory Findings

In the majority of trials submitted to this NDA, lab testing was only performed at screening. In trial 464, hematology and chemistry labs were obtained both at screening and throughout treatment, and there was no clinically meaningful differences observed between either SR group and placebo. Furthermore, trials conducted with SR for COPD revealed no concerning laboratory abnormalities associated with treatment.

7.4.3 Vital Signs

No clinically meaningful effects on heart rate or blood pressure were noted during the treatment period in the confirmatory trials. Additionally, no clinically significant differences in vital signs were observed with SR treatment during trials for COPD.

7.4.4 Electrocardiograms (ECGs)

In the majority of trials submitted to this NDA, 12-lead ECGs were only performed at screening. In trial 464, ECGs were obtained both at screening and end of treatment, and there was no clinically meaningful difference observed between either SR group and placebo. Furthermore, trials conducted with SR for COPD revealed no concerning abnormalities in ECG parameters or Holter monitoring.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were submitted or required.

7.4.6 Immunogenicity
Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events
For both frequency and time adjusted rates, there was a dose-dependent increase in many of the common AEs and anticholinergic effects as discussed previously. Furthermore, an analysis of the time-adjusted rates of asthma-related AEs in various safety populations favors SR 2.5 over SR 5 in adults, although both doses are better than placebo in all age groups. Similar results were seen regardless of how broadly asthma-related events were defined - asthma/asthma crisis versus all asthma-related PTs as listed in the table below. Because fewer patients with severe asthma received the 2.5 µg dose, an evaluation of moderate asthma patients is also included, and the results were consistent with the overall safety population.

Table 48. Time-adjusted Rates of Asthma-related AEs*

	Placebo		SR 2.5		SR 5	
	n(%) with event	Rate/100 pt-years	n(%) with event	Rate/100 pt-years	n(%) with event	Rate/100 pt-years
Overall safety population[1]	497 (31)	47.8	197 (19)	32.4	439 (27)	40.2
Adult safety population[2]	443 (34)	51.5	151 (19)	33.8	397 (29)	43.3
Adolescent safety population[3]	54 (20)	30.1	46 (18)	28.5	42 (16)	24.1
Moderate asthma population [4]	182 (23)	40.1	125 (19)	31.2	167 (21)	37.3

*Includes the following PTs: asthma, asthmatic crisis, bronchospasm, cough, dyspnea, dyspnea exertional
[1]Time at risk in patient-years: placebo=1040.1, SR 2.5=608.1, SR 5=1091.8
[2]Time at risk in patient-years: placebo=860.7, SR 2.5=446.6, SR 5=917.3
[3]Time at risk in patient-years: placebo=179.4, SR 2.5=161.5, SR 5=174.5
[4]Includes trials 418, 419, and 444. Time at risk in patient-years: placebo=453.6, SR 2.5=399.6, SR 5=447.7
Sources: SCS Supplement, Appendix 2, Tables 2.10.1.1; 2.10.1.3; 2.10.1.5; 2.10.1.7; 2.10.1.9; 2.10.1.11; 2.10.1.17; 2.10.1.19

7.5.2 Time Dependency for Adverse Events
The Applicant did not submit a specific analysis of safety data for time dependency and adverse events; however, anticholinergic side effects, such as dry mouth, were rarely reported in the shorter 12-week trials.

7.5.3 Drug-Demographic Interactions
The application included an analysis of adverse events by region (US/Canada, Europe , or Other), gender (male or female), age (adolescents, adults, or ≥ 65 years), race (American Indian/Alaskan Native, Asian, Black/African American, or White), smoking status (ex-smoker/second hand smoke exposure) and atopy (elevated serum IgE/ peripheral eosinophils). In general, the frequency and types of AEs reported in individual subgroups were similar to those observed in the overall safety populations as

presented in earlier sections of this review. Due to the international nature of this development program, an evaluation of racial subgroups was of particular interest, especially Black/African American subjects. As mentioned previously, the proportion of Black/African American subjects in the overall safety population (~3%) was much lower than the proportion of African Americans living in the United States (12-13%). However, the majority of Black/African American subjects in the clinical trial database were from the US/Canada (127 of 166 subjects). Although examination of racial subgroups was limited by the low number of Black/African American, there was no consistent pattern to suggest a differential safety profile in these populations.

7.5.4 Drug-Disease Interactions

The application included an analysis of adverse events based on history of cardiovascular disease as well as asthma severity and duration. There was no significant difference in overall AEs or cardiovascular AEs in those with a cardiac disease history. Relatively similar rates of types of AEs were seen across asthma disease severity or duration, although as would be expected, the number of asthma-related AEs reported had a positive correlation with increasing asthma severity. Additionally, patients with mild asthma reported more asthma-related AEs during treatment with SR 2.5 compared with SR 5; however, the patients from trial 442 contributed to a relatively small percentage of the overall number of asthma events.

7.5.5 Drug-Drug Interactions

No formal drug-drug interaction studies were included in this submission.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No specific studies were conducted to assess carcinogenicity in humans.

7.6.2 Human Reproduction and Pregnancy Data

No studies were conducted in pregnant women specifically. There was a single ectopic pregnancy reported in a patient treated with SR 2.5 µg and two spontaneous abortions reported in a placebo-treated patient and a salmeterol-treated patient.

7.6.3 Pediatrics and Assessment of Effects on Growth

The following section includes an analysis of adverse events in adolescent trials 444 and 456. The demographic profile and extent of exposure in the adolescent safety population was discussed previously.

Table 49 displays nonfatal SAEs in adolescents. Except for asthma, all of the SAEs occurred as single events. While the overall rate of SAEs in adolescents was relatively low, nominally more subjects in the SR treatment groups compared with placebo experienced an SAE. In contrast to the adult trials, the trend of fewer serious and

severe AEs due to asthma was not observed in adolescents. Moreover, the only asthma-related SAEs occurred in patients receiving SR 5 µg.

Table 49. Nonfatal SAEs in Adolescents

MedDRA SOC	MedDRA PT	Placebo N=273	SR 2.5 N=252	SR 5 N=264
Number of Unique Subjects with SAEs, n (%)		**2 (0.7)**	**3 (1)**	**5 (2)**
Gastrointestinal disorders	Abdominal pain upper	0	0	1 (0.4)
	Gastrointestinal disorder	0	1 (0.4)	0
	Peritoneal hemorrhage	0	1 (0.4)	0
	Retroperitoneal hematoma	0	1 (0.4)	0
Hepatobiliary disorders	Liver injury	0	1 (0.4)	0
Immune system disorders	Allergy to plants	0	0	1 (0.4)
	Anaphylactic reaction	0	0	1 (0.4)
Infections and infestations	Appendicitis	0	1 (0.4)	0
	Gastroenteritis	1 (0.4)	0	0
	Pyoderma	0	1 (0.4)	0
Injury, poisoning and procedural complications	Arterial injury	0	1 (0.4)	0
	Hepatic rupture	0	1 (0.4)	0
	Ligament sprain	0	0	1 (0.4)
	Multiple injuries	0	1 (0.4)	0
	Wound	0	1 (0.4)	0
Musculoskeletal and connective tissue disorders	Compartment syndrome	0	1 (0.4)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Teratoma	1 (0.4)	0	0
Respiratory, thoracic and mediastinal disorders	Asthma	0	0	2 (0.8)
Skin and subcutaneous tissue disorders	Dermatitis atopic	0	1 (0.4)	0

Abbreviations:SOC=System Organ Class, PT=Preferred Term, SR 2.5=tiotropium Respimat 2.5 µg/day, SR 5=tiotropium Respimat 5 µg/day
N=Treated Set, n=number of subjects reporting the adverse event
Source: Reviewer generated table in JReview using POPU (POPUDC=Treated set, POPUX does not equal "not treated", STUDY IN="205_444", "205_456"), AEAN1001 (CONDLVL=Preferred Term, ATONSLBL="MissTrtOnset", "Placebo", Postdb", "Post-study", "Post-treat", "Tio R2.5", or "Tio R5", AESERA=1)

Although no SAEs due to asthma occurred in the placebo groups, there were slightly more placebo patients who discontinued treatment due to worsening of asthma. The Applicant reported that no adverse dropouts occurred in the SR groups (Table 50). However, an analysis of the data revealed one patient receiving SR 2.5 µg, whose reason for discontinuation could reasonably have been categorized as worsening of asthma rather than lack of efficacy. This patient is detailed in Table 51.

Table 50. Dropout Profile: Incidence of Dropouts by Treatment Group and Reason for Adolescents

Reason for dropout	Placebo N=273	SR 2.5 N=252	SR 5 N=264
Prematurely discontinued, n (%)	9 (3.3)	11 (4.4)	5 (1.9)
Adverse Event	3 (1.1)	0	0
Worsening of asthma	2 (0.7)	0	0
Worsening of other pre-existing disease	0	0	0
Other AE	1 (0.4)	0	0
Lack of efficacy	0	1 (0.4)	0
Noncompliant with protocol	5 (1.8)	0	0
Lost to follow-up	0	0	0
Consent withdrawn not due to AE	0	4 (1.6)	1 (0.4)
Other	1 (0.4)	6 (2.4)	3 (1.1)

Includes trials 444 and 456
N=Treated Set
Source: SCS Supplement, Appendix 1, Table 2.5, p114

Table 51. Adverse Dropouts by Subject: Adolescents

Treatment Group, Subject ID	Age (yrs)	Sex	Race	Study Day of AE Start Date	Preferred Term	SAE	Intensity	Therapy	Recovery
SR 2.5 (N=252)									
444 1868	16	F	W	35*	Lack of Efficacy[1]	--	--	--	--
SR 5 (N=264)									
None	--	--	--	--	--	--	--	--	--
Placebo (N=273)									
444 2038	13	M	B	98	Asthma	No	Mild	Yes	Yes
444 3154	16	F	W	114	Asthma	No	Mild	No	Yes
456 2081	14	M	W	30	Palpitations	No	Moderate	No	Yes

Abbreviations: AE=adverse event, SAE=serious adverse event, SR 2.5=tiotropium Respimat 2.5 µg/day, SR 5=tiotropium Respimat 5 µg/day, F=female, M=male, W=White, B=Black, H=Hispanic/Latino
N=Treated Set
*Study day disposition term reported
[1]Reason for discontinuation described as "physical activity worsened"; no corresponding AE recorded
Source: Reviewer generated table in JReview using datasets POPU (POPUDC=Treated set, POPUX does not equal "not treated", STUDY IN="205_444", "205_456"), DS (EPOCH=Treatment Period), AEAN1001 (CONDLVL=Preferred Term, ATONSLBL="Placebo","Tio R2.5", or "Tio R5", AEACTA=3)

The majority of TEAEs graded as severe in intensity also met the regulatory definition for a serious adverse event; however, none of the severe AEs led to treatment discontinuation. Of note, two additional placebo subjects experienced severe asthma exacerbations that were not categorized as SAEs. The table below displays the severe TEAEs by number of subjects; note that some subjects had multiple severe TEAEs.

Table 52. Severe TEAEs in Adolescents

MedDRA SOC/PT	Placebo N=273	SR 2.5 N=252	SR 5 N=264
Number of unique subjects with severe TEAE, n (%)	**3 (1.1)**	**2 (0.8)**	**5 (1.9)**
Gastrointestinal disorders			
Abdominal pain upper	0	0	1 (0.4)*
Gastrointestinal disorder	0	1 (0.4)*	0
Peritoneal hemorrhage	0	1 (0.4)*	0
Retroperitoneal hematoma	0	1 (0.4)*	0
General disorders and administration site conditions			
Pyrexia	0	0	1 (0.4)
Hepatobiliary disorders			
Liver injury	0	1 (0.4)*	0
Injury, poisoning and procedural complications			
Arterial injury	0	1 (0.4)*	0
Hepatic rupture	0	1 (0.4)*	0
Multiple injuries	0	1 (0.4)*	0
Upper limb fracture	1 (0.4)	0	0
Wound	0	1 (0.4)*	0
Musculoskeletal and connective tissue disorders			
Compartment syndrome	0	1 (0.4)*	0
Respiratory, thoracic and mediastinal disorders			
Asthma	2 (0.7)	1 (0.4)	3 (1.1)*

*At least one event also met criteria for a serious adverse event
N=Treated Set, n=number of subjects with event
Source: Reviewer generated table in JReview using datasets POPU (POPUDC=Treated set, POPUX does not equal "not treated", STUDY IN="205_444", "205_456"), AEAN1001 (CONDLVL=Preferred Term, ATONSLBL="MissTrtOnset", "Placebo", Postdb", "Post-study", "Post-treat", "Tio R2.5", or "Tio R5", AEINT=3, AEONDTTM ≥1)

Regarding common AEs, very few occurred at a frequency of ≥1% in the SR groups and at a greater frequency than with placebo. Similar to the adult trials, abdominal pain and bronchitis were commonly reported AEs, and the overall incidence of asthma-related AEs of any severity (asthma, decreased PEF, wheezing, coughing, dyspnea, hypoxia, and bronchospasm) was lower in the SR groups as compared to placebo.

Table 53. Common TEAEs occurring ≥ 1% in SR groups (and greater than placebo): Adolescents

MedDRA SOC	MedDRA PT[1]	Placebo N=273	SR 2.5 N=252	SR 5 N=264
Number of unique subjects with any TEAE, n (%)		**130 (47.6)**	**121 (48.0)**	**127 (48.1)**
Gastrointestinal disorders	Abdominal pain, abdominal pain upper	2 (0.7)	1 (0.4)	4 (1.5)
Infections and infestations	Bronchitis, sinobronchitis	3 (1.1)	6 (2.4)	5 (1.9)
	Sinusitis, acute sinusitis	3 (1.1)	4 (1.6)	4 (1.5)
Nervous system disorders	Headache	4 (1.5)	8 (3.2)	11 (4.2)

Abbreviations:SOC=System Organ Class, PT=Preferred Term, SR 2.5=tiotropium Respimat 2.5 µg/day, SR 5=tiotropium Respimat 5 µg/day
N=Treated Set, n=number of subjects reporting the adverse event
[1]Related Preferred Terms, both within and across SOCs have been combined
Reviewer generated table in JReview using datasets POPU (POPUDC=Treated set, POPUX does not equal "not treated", STUDY IN="205_444", "205_456"), AEAN1001 (CONDLVL=Preferred Term, ATONSLBL="MissTrtOnset", "Placebo", Postdb", "Post-study", "Post-treat", "Tio R2.5", or "Tio R5", AEONDTTM ≥1)

As for adults, TEAEs that could have potentially been caused by the pharmacologic action of tiotropium were collected and analyzed using a time-adjusted rate difference between placebo and SR treatments. Overall, it appears that the frequency of potential anticholinergic side effects was relatively low; however, the dose-dependent increase in reactions such as dry mouth/throat or thirst observed in adults was not apparent here.

Table 54. Potential Drug Class-related Adverse Events in Adolescents

Preferred Term	Treatment Group and Time at Risk					
	Placebo 179 patient-years		SR 2.5 161 patient-years		SR 5 174 patient-years	
	n (%) with event	Rate/100 patient-years	n (%) with event	Rate/100 patient-years	n (%) with event	Rate/100 patient-years
Palpitations	1 (0.4)	0.6	0	0	0	0
Dry mouth	0	0	1 (0.4)	0.6	0	0
Constipation	1 (0.4)	0.6	0	0	0	0
Pyrexia	2 (0.7)	1.1	2 (0.8)	1.2	2 (0.8)	1.1
Dizziness	1 (0.4)	0.6	0	0	0	0

Includes trials 444 and 456
Source: Module 5.3.5.3, SCS Supplement, Appendix 2, Tables 2.10.1.9 and 2.10.1.11

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The Applicant provided no formal assessments of withdrawal and rebound. However, given the nature of the drug product and the low systemic bioavailability, drug abuse, withdrawal, and rebound are not expected. In the asthma development program, a maximum dose of SR 10 µg/day was evaluated in study 342; the only anticholinergic side effect reported was dry mouth. In addition, dose-ranging studies in COPD were conducted using doses up to 20 µg/day SR for 3 weeks with no major safety issues.

7.7 Additional Submissions / Safety Issues

The Applicant's 120-day safety update includes data from four pediatric clinical trials not included in the original NDA submission. The time period of data presented spans from trial initiation through August 27, 2014. The report includes unblinded data from one completed trial and pooled blinded data from three ongoing trials, which are summarized in the table below.

Table 55. Trials Included in 120-Day Safety Update

Completed Trial								
Trial No., Phase	**Last patient out**	**Population age group**	**Asthma severity**	**Description [Design]**	**Treatments: doses (µg)**	**Primary Endpoint(s)**	**Duration**	**No. of patients**
205.425, II	25 Sep 2012	6 to 11 years	Moderate	Efficacy and safety of tiotropium inhalation solution delivered via Respimat® inhaler once daily in the evening [R, DB, CO, PC]	Tio R1.25 Tio R2.5 Tio R5 Placebo	• FEV_1 peak within 3 hours post dosing	4 weeks	101
Ongoing Trials								
Trial No., Phase	**First patient enrolled**	**Population age group**	**Asthma severity**	**Description [Design]**	**Treatments: doses (µg)**	**Primary Endpoint(s)**	**Duration**	**Planned no. of patients**
205.443, II/III	26 Jul 2012	1 to 5 years	-	Safety and efficacy of tiotropium inhalation solution delivered via Respimat® inhaler once daily in the afternoon [R, DB, PG, PC]	Tio R2.5 Tio R5 Placebo	• Change from baseline in daytime asthma symptom score in the last week of the 12 week treatment period	12 weeks	102 (34 per arm)
205.445, III	03 Aug 2012	6 to 11 years	Moderate	Efficacy and safety of tiotropium inhalation solution delivered via Respimat® inhaler once daily in the evening [R, DB, PG, PC]	Tio R2.5 Tio R5 Placebo	• Peak FEV_1 response within 3 hours post dosing at the end of the 24-week treatment period	48 weeks	381 (127 per arm)
205.446, III	24 Jul 2012	6 to 11 years	Severe	Efficacy and safety of tiotropium inhalation solution delivered via Respimat® inhaler once daily in the evening [R, DB, PG, PC]	Tio R2.5 Tio R5 Placebo	• Peak FEV1 response within 3 hours post dosing at the end of the 12-week treatment period	12 weeks	375 (125 per arm)

R = randomised; DB = double-blind; PC = placebo controlled; CO = cross-over; PG = parallel group

Source: 4-month safety report

In the completed trial (205.425), 101 subjects ages 6 to 11 years of age were randomized and treated with study medication. Approximately 10% of subjects from each treatment group experienced an AE, the most common (≥ 2 subjects) being nasopharyngitis, rhinitis, bronchitis, influenza, asthma, cough, and headache. There were no severe AEs, AE's leading to discontinuation, deaths or nonfatal SAEs.

In the three ongoing trials (205.443, 205.445, 205.446), a total of 733 pediatric subjects have been treated and included in the pooled safety analysis. Of these subjects, 343 (47%) have reported at least one TEAE, the most common (≥ 5%) of which were asthma, decreased peak expiratory flow, nasopharyngitis, and viral respiratory tract infection. A total of 17 (2%) SAEs have been reported, nine of which were asthma-related and three of which were appendicitis. The remainder of SAEs were single events. To date, there have been no treatment discontinuations due to an AE or deaths in any of the these trials.

The information reported in the 120-day safety update is consistent with the adult and adolescent clinical trial data submitted to the original NDA and does not reveal any new safety concerns.

8 Postmarket Experience

SR 5 µg/day was approved in the U.S. for COPD on September 24, 2014 and has been marketed in Europe for COPD since 2007. Additionally, SHH for COPD was approved in Europe and the U.S. in 2001 and 2004, respectively. Although SR received marketing authorization for adults with asthma from the EMA in September 2014, the data lock

point for the Applicant's post-marketing safety report occurred prior to approval for this indication.

From October 1, 2001 through September 30, 2013, the cumulative marketed patient exposure is estimated to be (b) (4) patient-years for SR and (b) (4) patient-years for SHH. A query of BI's Global Pharmacovigilance Database for case reports containing an indication for the PT "asthma" during this time period revealed a total of 3509 individual case reports: 88 for SR, 2269 for SHH, and 1158 for Spiriva Unassigned or not otherwise specified. Regarding the SR case reports, only one involved a known pediatric patient (≤ 10 years of age); however, 36 cases did not contain a reported age. The most frequently reported AEs for SR were off-label use, cough, dry mouth, medication error, pneumonia, dysphonia, and drug ineffective. Overall, findings were similar to those in the controlled clinical trials, and analysis of the postmarketing safety data did not reveal any new safety concerns.

9 Appendices

9.1 Literature Review/References

The application included a listing of references but no systematic literature review. A PubMed search [search terms: tiotropium AND asthma; no limits] yielded 186 references. These articles were reviewed briefly, many of which were publications of the clinical trials reviewed in this NDA, but no new information was identified that would change the risk/benefit assessment.

References

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3. The Global Strategy for Diagnosis, Management, and Prevention of COPD (updated 2015) available on the GOLD website, www.goldcopd.org
4. Kerstjens HA, et al. Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med.* 2012 Sep 27; 367 (13): 1198-207
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9.2 Labeling Recommendations

Labeling discussions were ongoing at the time of this review.

9.3 Advisory Committee Meeting

The Pulmonary and Allergy Drug Advisory Committee (PADAC) did not convene for this application because SR is already commercially available and because there was general agreement between the Applicant and the Agency regarding the overall efficacy and safety data in the proposed population of asthma patients, notwithstanding disagreement regarding the correct dose for patients with asthma.

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/s/

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