CLINICAL REVIEW

Application Type	Efficacy Supplement
Application Number(s)	NDA 21-936/S-007
Priority or Standard	Priority
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Division / Office	DPARP / ODEII
Reviewer Name(s)	Stacy Chin, MD
Review Completion Date	January 18, 2017
Established Name	Tiotropium (b) (4)
(Proposed) Trade Name	Spiriva Respimat
Therapeutic Class	Anticholinergic
Applicant	Boeringher Ingelheim
Formulation(s)	Inhalation Solution
Dosing Regimen	2.5 µg daily
Indication(s)	Asthma
Intended Population(s)	(b) (4) to 11 years of age

Template Version: March 6, 2009

Table of Contents

Table of Tables

Table of Figures

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, once-daily maintenance treatment of asthma in patients 6 to 11 years of age. (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 tiotropium Respimat, a long-acting muscarinic antagonist, for the long-term, once-daily, maintenance treatment of asthma in patients 6 to 11 years of age. (b) (4)

While the determination of efficacy was based on partial extrapolation of efficacy in adults and adolescents with asthma, the primary clinical data submitted to support the efficacy and safety of tiotropium Respimat (TioR) for the indication of long-term, once-daily, maintenance treatment of asthma in the proposed pediatric age group of (b) (4) to 11 year old patients consisted of two efficacy and safety trials in patients 6 to 11 years of age and one safety trial in patients 1 to 5 years of age. All trials were randomized, double-blind, placebo-controlled, and parallel group in design and evaluated two doses of TioR, 2.5 µg and 5 µg administered once daily.

In 12 and 48 week trials of 6 to 11 year old patients with asthma, bronchodilator activity was measured by peak FEV_1 measured within 3 hours post-dose (FEV_1 $peak_{(0-3)}$) and trough FEV_1, designated as primary and key secondary endpoints, respectively. TioR 2.5 µg once daily demonstrated statistically significant improvements in FEV_1 $peak_{(0-3)}$ and trough response in one trial, while the higher dose of TioR, 5 µg once daily, demonstrated statistically significant responses in FEV_1 $peak_{(0-3)}$ and trough compared to placebo in both trials. Neither trial showed statistically significant effects on patient or caretaker-reported outcomes such as the ACQ-IA, PAQLQ, or asthma symptom score or in rescue medication use. Regarding asthma exacerbations, there were a similar number of events across treatment groups in the 48-week trial, but fewer events with TioR 2.5 in the 12-week trial.

TioR 2.5, the approved dose for asthma, demonstrated significant improvements in lung function in one of the two trials.. However, the results from the positive 48 week trial were consistent with spirometric data from the adult and adolescent asthma development program which consistently indicated that TioR 2.5 had an equivalent, if not improved, bronchodilator treatment effect compared to TioR 5 with similar effects on

reduction of asthma exacerbations. Given that efficacy of TioR in the proposed 6 to 11 year old age group is partially based on extrapolation of efficacy in adults and adolescents, TioR 2.5 once daily still appears to be the most appropriate dose for this age group for the treatment of persistent asthma on top of ICS therapy.

In 1 to 5 year old patients, there was a single 12-week safety trial in patients with persistent asthma. (b) (4)

With respect to safety, there were no major safety concerns or new safety signals identified in either the 6 to 11 year old or 1 to 5 year old population. In general, TioR demonstrated a similar safety profile in pediatric asthma patients to that observed in adults and adolescents with asthma. 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, reports of systemic anticholinergic effects, such as dry mouth, were rare.

In conclusion, the risk-benefit assessment for TioR 2.5 µg once daily as a bronchodilator maintenance treatment in patients 6 to 11 years of age with asthma is favorable, and thus approval in this age group is recommended. (b) (4)

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

There are no recommendations for additional postmarket requirements or commitments. This submission fulfills the PREA required studies and Written Request.

2 Introduction and Regulatory Background

2.1 Product Information

The active component of tiotropium (trade name Spiriva) Respimat is tiotropium bromide monohydrate, a long-acting antimuscarinic (or anticholinergic) drug. The tiotropium Respimat (TioR) drug product consists of an aqueous solution of tiotropium delivered via oral inhalation using the Respimat device. Each actuation from the TioR inhaler delivers 2.5 µg of tiotropium (equivalent to 3.124 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, and on September 15, 2015, at a dose of 2.5 µg/day for the long-term, once-daily, maintenance treatment of asthma in patients 12 years of age and older.

In this supplemental NDA, the proposed indication is for the long-term, once-daily, maintenance treatment of asthma in patients (b) (4) of age and older at the same 2.5 µg once daily dose (2 actuations of 1.25 µg).

2.2 Tables of Currently Available Treatments for Proposed Indications

For persistent asthma in pediatric patients less than 12 years of age, 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 and listed in the table below. Listed products not approved in patients < 12 years of age are denoted with an asterisk since there is the potential for off-label use in younger patients. In addition, note that use of long-acting beta agonists without a concomitant inhaled corticosteroid is currently contraindicated due to an increase in asthma-related deaths observed in clinical trials. While ipratropium bromide is frequently used off-label to treat acute asthma exacerbations in pediatric patients, there are currently no anticholinergic agents approved for the maintenance treatment of asthma in this age group.

Table 1. Currently Available Therapies for the Maintenance Treatment of Asthma in Patients < 12 Years of Age

Drug Class	Generic Name	Brand Name
Inhaled corticosteroids	Fluticasone furoate DPI*	Arnuity Ellipta
	Beclomethasone diproprionate HFA	QVAR
	Budesonide DPI and respules	Pulmicort
	Fluticasone propionate HFA and Diskus	Flovent
	Mometasone HFA* and DPI	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
Anticholinergic	Tiotropium bromide inhalation solution*	Spiriva Respimat
Immunomodulators	Omalizumab (Anti-IgE mAb)	Xolair
	Mepolizumab (Anti-IL-5 mAb)*	Nucala
	Reslizumab (Anti-IL-5 mAb)*	Cinqair
Leukotriene modifiers	Montelukast	Singulair
	Zafirlukast	Accolate
	Zileuton*	Zyflo
Xanthines	Theophylline	multiple

Abbreviations: DPI=dry powder inhaler, HFA=hydrofluoroalkane, mAb=monoclonal antibody
*Approved indication does not include patients < 12 years of age

2.3 Availability of Proposed Active Ingredient in the United States

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

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].

[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-

2.5 Summary of Presubmission Regulatory Activity Related to Submission

September 15, 2015

- Approval of Spiriva Respimat 2.5 µg once daily for the long-term maintenance treatment of asthma in patients 12 years of age and older
- Approval letter outlined two PREA-required studies:
    - 2953-1: Conduct a 12-week, randomized, double-blind, parallel-group, placebo-controlled, efficacy and safety study of tiotropium delivered via the Respimat device in children 6-11 years of age with asthma. The study should evaluate at least two doses of tiotropium and include approximately 125 patients per treatment arm.
    - 2953-2: Conduct a 48-week, randomized, double-blind, parallel-group, placebo-controlled, efficacy and safety study of tiotropium delivered via the Respimat device in children 6 to 11 years of age with asthma. The study should evaluate at least two doses of tiotropium and include approximately 125 patients per treatment arm.

October 19, 2015

- Boeringher Ingelheim (BI) submitted a PPSR which included three studies in 6 to 11 year old patients and one study in 1 to 5 year old patients; all but one study had already been completed with final study reports submitted to the Agency.

February 12, 2016

- The Agency issued a Written Request outlining the following studies
    - Study 1: An in vitro characterization study of the dose delivery from the Respimat inhaler with at least one U.S.-marketed spacer
    - Study 2: A double-blind, randomized, parallel group, placebo-controlled, efficacy and safety study in children ages 6 to 11 years with asthma who are symptomatic despite maintenance therapy with a stable medium-dose ICS either alone or in combination with another controller medication (e.g., LABA or leukotriene modifier). The duration must be at least 48 weeks, and the study must include at least two doses of tiotropium bromide inhalation solution.

Reviewer comment: Of note, the Agency did not require studies in patients 1 to 5 years of age for either PREA or the Written Request because 1) persistent asthma, as opposed to transient wheeze, is difficult to diagnose at this age and 2) administration of inhalation products with a spacer device, which is required in this age group, constitutes a new product due to changes in the delivery characteristics of the drug.

AllergyDrugsAdvisoryCommittee/UCM416247.pdf

2.6 Other Relevant Background Information

The TioR pediatric asthma clinical development program in patients < 12 years of age was initiated prior to approval of the asthma indication in adults and adolescents and without input from the Agency.

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.

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*. None of the investigators reported disclosable financial interests. 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. Thus, there are no financial conflict of interest-related concerns that raise questions about the integrity of the data.

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 138		
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): 0		
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: 0 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 ☒ N/A
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ N/A
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☒ N/A

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

As part of the Written Request, the Applicant conducted *in vitro* experiments characterizing the performance of TioR when coupled with a commercially available valved holding chamber (VHC), aka spacer. For this study, the Applicant used the Trudell AeroChamber Plus Flow Vu Antistatic Valved Holding Chamber and Facemask (small and medium sizes) and commercial Spiriva Respimat at the approved dose for asthma (2 actuations of 1.25 µg). The objective was to evaluate the particle size distribution of the dose delivered into a cascade impactor from the Respimat/VHC combination compared to the Respimat device alone. The aerosolized drug generated by the Respimat inhaler passing through the VHC was evaluated based on cascade impactor measurements with pediatric flow rates of 4.9, 8.0, and 12.0 L/min and four defined holding times (i.e., time between actuation of the Respimat inhaler and start of inhalation from the VHC).

In general, the fine particle dose through the VHC decreased as the holding time increased due to aerosol deposition in the VHC. (b) (4)

(b) (4)

Overall, the fine particle fraction across flow rates and delay times was 69-89% of the delivered dose through the VHC.

Experiments to evaluate the effect of cleaning the VHC demonstrated that dose delivery from the VHC is not impacted by cleaning status (i.e., new and unwashed, used and washed, 1 week of use without cleaning, used after 50 cleaning cycles).

For additional details, refer to the CMC review by Dr. Chong Ho Kim.

4.2 Clinical Microbiology

No new clinical microbiology data was submitted or required.

4.3 Nonclinical Pharmacology/Toxicology

No new nonclinical data was submitted or required.

4.4 Clinical Pharmacology

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.

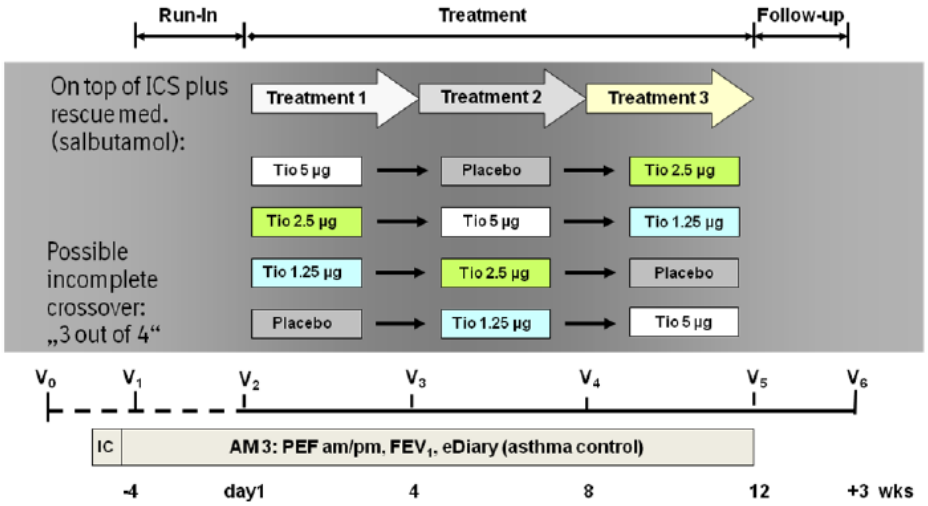
4.4.2 Pharmacodynamics

For the pediatric asthma clinical development program, the Applicant conducted a double-blind, placebo-controlled, incomplete crossover, dose-ranging study in 6 to 11 year old patients (Study 205.425). The once daily dosing interval was established in the asthma development program for adults.

In Study 205.425, the Applicant explored nominal doses of 1.25, 2.5, and 5 µg administered once daily for 4 week treatment periods. Dose selection for this study was primarily based upon the approved dose in COPD (5 µg) and phase 3 asthma studies in adults and adolescents which evaluated doses of 2.5 and 5 µg once daily. The study enrolled children 6 to 11 years of age with moderate persistent asthma. At enrollment, these patients had a minimum 6 month history of asthma, demonstrated bronchodilator reversibility resulting in FEV_1 increase ≥ 12%, and were symptomatic/uncontrolled (defined by an ACQ score ≥ 1.5) despite maintenance treatment with medium dose ICS either alone or in combination with a LABA or leukotriene modifier. During the trial,

patients continued their regular ICS medication; leukotriene modifiers were permitted throughout the trial, but LABAs had to be discontinued 24 hours before Visit 1. A schematic of the study design is shown in Figure 1. There was no washout period between treatment periods; therefore, baseline values were measurements obtained prior to the first dose of randomized treatment in the first period.

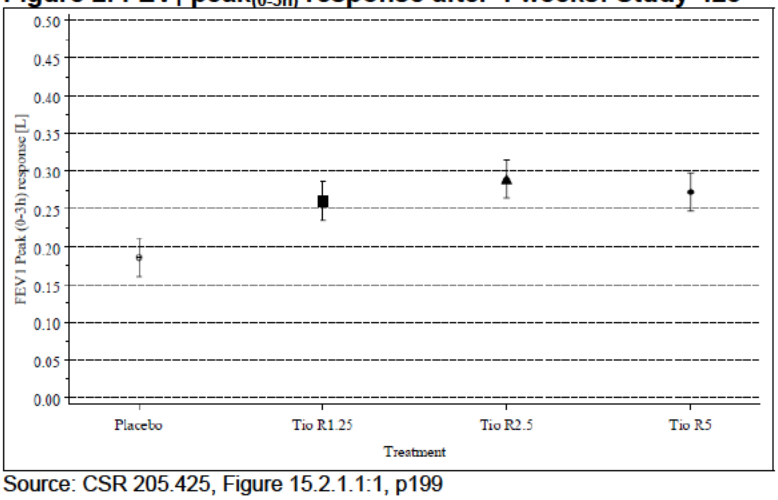
Figure 1. Study Schematic: Study 425



Source: Clinical Trial Protocol 205.425, Figure 9.1:1, p39

The primary efficacy endpoint was FEV_1 $peak_{(0\text{-}3h)}$ response, determined at the end of each 4-week treatment period. FEV_1 $peak_{(0\text{-}3h)}$ was defined as the maximum FEV_1 measured within the first 3 hours post-dose. FEV_1 $peak_{(0\text{-}3h)}$ response was defined as the difference of FEV_1 $peak_{(0\text{-}3h)}$ and the FEV_1 baseline measurement at Visit 2. The mean baseline FEV_1 value at Visit 2 for all patients treated with at least one dose of study medication (Full Analysis Set, FAS) was 1.638 L. The adjusted mean FEV_1 $peak_{(0\text{-}3h)}$ response after 4 weeks of treatment was 0.185 L for placebo, 0.261 L for TioR 1.25 µg, 0.290 L for TioR 2.5 µg, and 0.272 L for TioR 5 µg. Although all tiotropium doses demonstrated a statistically significant increase in FEV_1 $peak_{(0\text{-}3h)}$ over placebo, there was no dose-dependent response, suggesting that TioR 2.5 remains the correct dose in this age group (Figure 2).

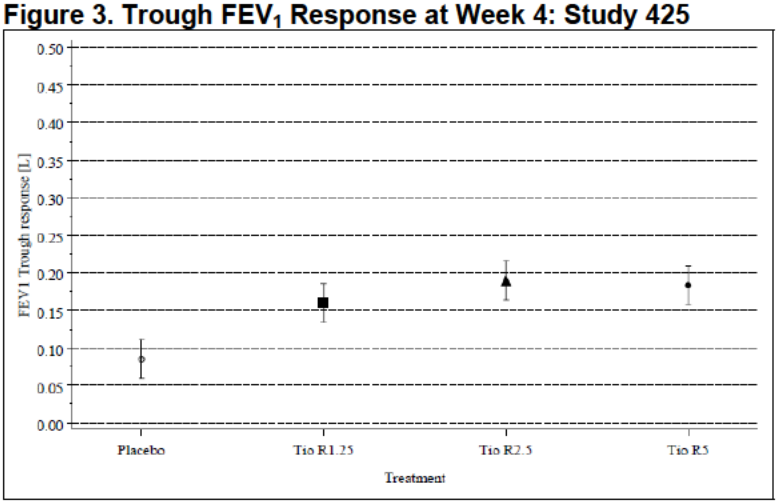
Figure 2. FEV_1 $peak_{(0-3h)}$ response after 4 weeks: Study 425



Source: CSR 205.425, Figure 15.2.1.1:1, p199

With regard to the secondary endpoint of trough FEV_1 response after 4 weeks of treatment, active treatment with TioR resulted in statistically significant increases over placebo; however, results were again similar for all tiotropium doses. Adjusted mean trough FEV_1 at 4 weeks was 0.085 L for placebo, 0.160 L for TioR 1.25 µg, 0.190 L for TioR 2.5 µg, and 0.183 L for TioR 5 µg (Figure 3).

Figure 3. Trough FEV_1 Response at Week 4: Study 425



Source: Clinical Study Report 205.425, Figure 15.2.1.2.1:1, p204

Given the results, there was adequate support for carrying forward the 2.5 µg and 5 µg doses to phase 3 trials in 6 to 11 year patients; however, it should be noted that the pediatric studies were initiated prior to approval of TioR for the maintenance treatment of asthma in adults and adolescents. (b) (4) efficacy data ultimately supported approval of the lower 2.5 µg once daily dose for the asthma indication.

4.4.3 Pharmacokinetics

PK samples were collected in two of the four submitted studies: blood and urine in Study 205.425 and urine in Study 205.443. PK results from Study 205.425 in 6 to 11 year old patients showed that mean steady state and mean urine excretion fraction of unchanged tiotropium within 24 hours post-dose following a 4-week treatment period with TioR 2.5 were comparable to measurements observed in adults with asthma treated with the same dose regimen. PK results from Study 204.443 in 1 to 5 year old patients showed that at steady state approximately 1.08% of the inhalation dose was excreted unchanged in the urine within 3 hours post-dose following treatment with TioR 2.5 compared to 2.61% in adults. However, without corresponding tiotropium plasma concentrations and urine samples collected over a longer period, the systemic exposure of tiotropium in children 1 to 5 years of age is unknown and the significance of the lower urine excretion fraction after 3 hours is unclear. Refer to the clinical pharmacology review by Dr. Yunzhao Ren for further details.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

All of the trials conducted in the pediatric asthma development program for TioR are summarized in Table 2. Because all trials included the same "205" prefix, this review refers to an individual trial by the last 3 digits only. There was one dose-ranging study in patients 6 to 11 years of age, Study 425. The results from this study along with the expectation that the 5 µg daily dose would be approved for the asthma indication in adults and adolescents formed the basis for dose selection in phase 3 trials; results from Study 425 were discussed in Section 4.4.2. In addition to partial extrapolation of efficacy from adults, the information to support the efficacy and safety of TioR for the long-term maintenance treatment of asthma in patients 1 to 11 years of age is derived from three trials: 445, 446, and 443. 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.

Table 2. Pediatric Trials

Trial (dates)	Design	Population	Background Medication	Treatment	N	Duration	Primary Endpoint(s)	Sites (countries)
Phase 2 and 3 trials in 6 to 11 year olds								
205.425 *(8//11-9/12)*	R, DB, PC, IXO	6-11 years, moderate asthma	Medium-dose ICS ± LABA/LTRA	TR 1.25 QD TR 2.5 QD TR 5 QD Placebo	75 74 76 76	12 weeks (4 week treatment periods)	FEV_1 $peak_{0-3h}$	24 sites[(a)]
205.445 *(6/12-12/15)*	R, DB, PC, PG	6-11 years, moderate asthma	Medium-dose ICS ± LABA/LTRA	TR 2.5 QD TR 5 QD Placebo	135 135 131	48 weeks	FEV_1 $peak_{0-3h}$ *Trough FEV_1	79 sites[(b)]
205.446	R, DB, PC, PG	6-11 years severe	High-dose ICS + 1 controller	TR 2.5 QD TR 5 QD	136 130	12 weeks	FEV_1 $peak_{0-3h}$ *Trough FEV_1	92 sites[(c)]

Trial (dates)	Design	Population	Background Medication	Treatment	N	Duration	Primary Endpoint(s)	Sites (countries)
(7/12-5/15)		asthma	OR medium- dose ICS + 2 controllers	Placebo	134			
Phase 3 safety trial in 1 to 5 year olds								
205.443 *(7/12-12/14)*	R, DB, PC, PG	1-5 years, persistent asthma	Any dose ICS	TR 2.5 QD TR 5 QD Placebo	36 31 34	12 weeks	Combined daytime symptom score from the Pediatric Caregiver Diary	32 sites[(d)]

Abbreviations: R=randomized, DB=double-blind, PC=placebo-controlled, PG=parallel group, IXO=incomplete crossover, ICS=inhaled corticosteroid, LABA=long-acting beta-agonist, LTRA=leukotriene receptor antagonist, TR=Tiotropium Respimat, QD=once daily, UK=United Kingdom, USA=United States of America
N=randomized subjects
* Key secondary endpoint
[a] Germany, Hungary, Latvia, Lithuania, Russia, Ukraine
[b] Bulgaria, Canada, Germany, Guatemala, Hungary, Korea, Latvia, Lithuania, Norway, Portugal, Romania, Russia, Sweden, Ukraine, UK, USA
[c] Argentina, Australia, Belgium, Brazil, Canada, Czech Republic, Germany, Guatemala, Hungary, Latvia, Lithuania, Poland, Romania, Russia, Slovakia, Ukraine, USA
[d] Belgium, Finland, Germany, Korea, Latvia, Lithuania, Malaysia, Netherlands, Philippines, Ukraine, USA
Source: Module 2.7.6, Synopses of Individual Studies

5.2 Review Strategy

This review focuses on the phase 3 trials in patients 1 to 11 years of age.

5.3 Discussion of Individual Studies/Clinical Trials

The two phase 3 trials in 6 to 11 year old patients (Studies 445 and 446) were similar in design with the main differences being duration (48 weeks vs 12 weeks), asthma severity (moderate vs severe), and concomitant background therapy. Therefore, Study 445 is described in detail below while the description of Study 446 has been abbreviated to note only the differences between studies.

Study Number	205.445
Title	A randomized, double-blind, placebo-controlled, parallel-group trial to evaluate efficacy and safety of tiotropium inhalation solution (2.5 µg and 5 µg) delivered via Respimat inhaler once daily in the evening over 48 weeks in children (6 to 11 years old) with moderate persistent asthma
Study dates	August 6, 2012 – December 8, 2015
Study report	March 11, 2016
Sites	79 sites in 16 countries

Amendments
The first global protocol amendment, dated March 21, 2013, included clarification of the exclusion criteria to state that patients who had experienced an asthma exacerbation or respiratory infection between visits 1 and 2 are not excluded if visit 2 is postponed until

4 weeks after recovery. The second global amendment, dated April 1, 2015, added the following variables as further efficacy endpoints: individual FEF_{25-75} response at each time point and visit, FEV_1 $peak_{0-3}$ and trough FEV_1 each expressed as a percentage of the patient's predicted FEV_1 after 24 and 48 weeks of treatment, time to first symptomatic asthma exacerbation, and ACQ-IA6. Other revisions included in the amendments primarily consisted of clarifying language or administrative changes.

Objectives

The primary objective of the trial was to demonstrate superiority of tiotropium (5 µg and possibly 2.5 µg once daily in the evening) over placebo with regard to the primary pulmonary function endpoint after 24 weeks of treatment in 6 to 11 year old patients with moderate persistent asthma. Secondary objectives were to evaluate efficacy of tiotropium with regard to other efficacy endpoints after 24 and 48 weeks of treatment and to evaluate the long-term safety of tiotropium with 48 weeks of treatment compared to placebo.

Study Design

This was a randomized, double-blind, placebo-controlled, parallel group trial designed to assess the efficacy and safety of two doses of tiotropium inhalation solution delivered via Respimat inhaler (2.5 and 5 µg once daily in the evening) over 48 weeks in children 6 to 11 years of age with moderate persistent asthma who were uncontrolled on a background therapy of medium dose inhaled corticosteroids.

After collection of informed consent/assent at Visit 0 and an initial screening visit (Visit 1), patients entered a 4-week screening period. The screening period consisted of twice daily use of the AM3 device to measure peak expiratory flow rates and record asthma symptoms and medication use. Patients who continued to meet all inclusion criteria and none of the exclusion criteria at the end of the screening period (Visit 2) were randomized to receive either 2.5 µg or 5 µg TioR or matching placebo for a 48 week treatment period. Study visits occurred at weeks 12, 24, 36, 48, and 51. In between study visits, patients/caregivers were contacted by telephone at 6, 18, 30, and 42 weeks after randomization. After 24 weeks (Visit 4), the efficacy endpoints were measured for the primary statistical analysis, but patients continued blinded treatment for an additional 24 weeks. At the end of the treatment period (Visit 6), patients entered a 3-week follow-up period followed by a final study visit (Visit 7).

Patient Population

A total of 381 patients (~127 per arm) were to be enrolled in the trial; individual study sites were expected to enroll 4 to 5 patients on average.

Key Inclusion Criteria

1. Male or female patients 6 to 11 years of age on the date of informed consent/assent
2. At least a 6 month history of asthma at the time of enrollment

3. Maintenance treatment with a medium dose of inhaled corticosteroid (see Table 4) with or without concomitant controller medications (i.e., LABA or leukotriene modifier) for at least 4 weeks prior to Visit 1. However, LABAs must be discontinued 24 hours prior to Visit 1 and are not permitted during the study; leukotriene modifiers may be continued during the study treatment period.
4. Symptomatic, defined as ACQ-IA mean score ≥ 1.5, at Visits 1 and 2 prior to randomization
5. Pre-bronchodilator FEV_1 ≥ 60% and ≤ 90% predicted normal at Visit 1
6. Bronchodilator reversibility, defined as increase in FEV_1 ≥ 12% 15 to 30 minutes after 200 µg albuterol/salbutamol at Visit 1
7. Variation in absolute pre-bronchodilator FEV_1 values within ± 30% between Visits 1 and 2
8. Ability to use the Respimat inhaler correctly and to perform all trial related procedures (electronic diary compliance of at least 80% required)

Exclusion criteria

1. Acute asthma exacerbation or respiratory infection within 4 weeks prior to Visit 1 or Visit 2
2. Requiring 6 or more puffs of rescue medication a day for more than 2 consecutive days within 4 weeks of Visit 1 or Visit 2
3. Significant disease other than asthma (e.g., cystic fibrosis). A significant disease defined as a disease, which in the opinion of the investigator, may the put the patient at risk from participation, influence the results of the trial, or cause concern regarding the patient's ability to participate in the trial.
4. Clinically relevant abnormal hematology or chemistry lab values at screening
5. Prior history of congenital or acquired cardiac disease or hospitalization for cardiac syncope or failure in the past year
6. Cardiac arrhythmia that is unstable or life-threatening in the opinion of the investigator or that has required intervention or a change in drug therapy in the past year
7. Malignancy for which the patient has undergone radiation, resection, or chemotherapy in the past year
8. Active tuberculosis
9. Thoracotomy with pulmonary resection
10. Pulmonary rehabilitation program participation either currently or within 6 weeks prior to Visit 1
11. Pregnancy or lactation
12. Known hypersensitivity to anticholinergics, BAC, EDTA, or any of the other components of the tiotropium inhalation solution
13. Post-menarchal females of child-bearing potential not using highly effective forms of contraception (abstinence considered a highly effective method).
14. Anti-IgE treatment within 6 months prior to Visit 1 and/or during the screening period
15. Systemic corticosteroids or beta-adrenergics within 4 weeks of Visit 1

16. Oral beta-blocker medication within 4 weeks prior to Visit 1 and/or during the screening period
17. Treatment with long-acting or systemic anticholinergics or theophylline within 4 weeks prior to Visit 1 and/or during the screening period or with short-acting anticholinergics or theophylline within 2 weeks prior to Visit 1
18. Treatment with non-approved or experimental asthma therapies within 4 weeks prior to Visit 1 and/or during the screening period
19. Investigational drug use within 6 half-lives or 4 weeks (whichever is longer) of Visit 1 or during the screening period
20. Previous randomization into this trial or current participation in another trial
21. Narrow angle glaucoma or any other disease in which anticholinergics are contraindicated
22. Moderate to severe renal impairment, defined as creatinine clearance < 50 mL/min
23. Inability to comply with medication restrictions prior to Visits 1 and 2

Concomitant and Prohibited Medications

The following table lists required, permitted, and prohibited concomitant medications along with the required washout periods.

Table 3. Overview of required, permitted, and restricted medication

Drug Class	Sub-class	Study Period		
		Screening Period	Treatment Period	Follow-up Period
Corticosteroids	Inhaled corticosteroids	REQUIRED	REQUIRED	REQUIRED
	Systemic (e.g. oral or i.v.) corticosteroids	not permitted[1]	not permitted (except for treatment of asthma exacerbation)	not permitted
	Topical (e.g.intranasal) corticosteroids (e.g. Nasonex®)	permitted	permitted	permitted
Beta-adrenergics	Inhaled short-acting β_2-agonists	rescue	rescue	permitted
	Inhaled long-acting β_2-agonists	not permitted[4]	not permitted	permitted
	Systemic (e.g. oral or i.v. or s.c.) β_2-agonists (cave: this includes Spasmo Mucosolvan®)	not permitted[1]	not permitted (except for treatment of asthma exacerbation)	not permitted
Beta blockers	Beta blockers (oral or i.v.) (e.g. Inderal®) (except topical eye medications)	not permitted[1]	not permitted	not permitted
Anticholinergics	Inhaled short-acting anticholinergics (inhalation aerosol and nasal spray) (e.g. Atrovent®)	not permitted[2]	not permitted (except for treatment of asthma exacerbation)	permitted
	Inhaled long-acting anticholinergics(e.g. Spiriva®)	not permitted[1]	Study medication	not permitted
	Systemic (s.c., i.v. or oral) anticholinergics, e.g. spasmolytics, muscle relaxants	not permitted[1]	not permitted	not permitted
Combination medications	Combination iCS/ long- acting β_2-agonist (e.g. Advair®/ Seretide®, Symbicort®)	not permitted[8]	not permitted	permitted
	Combination iCS/ short-acting β_2-agonist (e.g. Butasol®)	not permitted[7]	not permitted	permitted
	Combination short-acting anticholinergic/ short-acting β_2-agonist (e.g. Berodual®, Combivent®, Duovent®)	not permitted[2]	not permitted	permitted
Methylxanthines	Short acting theophillines (e.g. Theolair®)	not permitted [2]	not permitted (except for treatment of asthma exacerbation)	not permitted
	Long acting theophillines (e.g. Theolair® retard)	not permitted[1]	not permitted	not permitted
Miscellaneous	Other investigational drugs	not permitted[6]	not permitted	not permitted
	Leucotrienemodifiers (e.g.montelukast Singulair®)	permitted[5]	permitted	permitted
	Anti-IgE treatment (e.g. omalizumab, Xolair®)	not permitted[3]	not permitted	not permitted
	Cromones (e.g. sodium cromoglycate, nedocromil sodium)	permitted[5]	permitted	permitted
	Antihistamines	permitted	permitted	permitted
	Mucolytics (not containing bronchodilators)	permitted	permitted	permitted
	Experimental, non-approved asthma medications (e.g. TNFα-blockers)[9]	not permitted[1]	not permitted	not permitted

1. Not permitted within 4 weeks prior to Visit 1
2. Not permitted within 2 weeks prior to Visit 1
3. Not permitted within 6 months prior to Visit 1
4. To be stopped at least 24 hours prior to Visit 1.
5. To be stabilised for at least 4 weeks prior to the trial and stable throughout the trial.
6. Washout of at least one month or six half lives (whichever is greater)
7. To be switched to the inhaled steroid mono-product without changing the steroid dose, at least 8 hours prior to Visit 1
8. to be switched to the inhaled steroid mono-product without changing the steroid dose, at least 24 hours prior to Visit 1
9. Non-approved and according to international guidelines (e.g. GINA guidelines 2010 [P11-06175]) not recommended 'experimental' drugs for routine asthma therapy (e.g. TNF-alpha blockers, methotrexate, cyclosporine).

Source: Clinical trial protocol 205.445, Table 4.2.2.1:1, p52

Table 4. Estimated equipotent daily doses of inhaled corticortisteroids for children > 5 years

Drug Name	Medium daily dose (µg)
Beclomethasone dipropriate	≥ 200 to ≤ 400
Budesonide	≥ 200 to ≤ 400
Budesonide-Neb	≥500 to ≤ 1000
Ciclesonide	≥160 to ≤ 320
Flunisolide	≥ 750 to ≤ 1250
Fluticasone propionate	≥ 200 to ≤ 500
Mometasone furoate	≥ 200 ≤ 400
Triamcinolone acetonide	≥ 800 ≤ 1200

Source: Clinical trial protocol 205.445, Table 10.3:1, p110

Study Treatments

At Visit 2, subjects were randomized equally to one of three blinded treatment arms:

- 2.5 µg tiotropium inhalation solution daily (2 actuations of 1.25 µg)
- 5 µg tiotropium inhalation solution daily (2 actuations of 2.5 µg)
- Placebo inhalation solution daily (2 actuations)

All study treatments were orally inhaled via the Respimat inhaler between 4 p.m. and 7 p.m.

Efficacy Assessments

This section describes the efficacy variables evaluated in the trial. Refer to Table 5 for the timing of assessments.

Pulmonary Function Testing (PFTs)

Spirometry was performed with the patient in a seated position and measurements were obtained in triplicate. The highest FEV_1 and FVC were recorded regardless of whether or not they came from the same or different spirometric maneuvers. The $FEF_{25-75\%}$ was taken from the blow with the largest sum of FEV_1 and FVC. At Visit 2, baseline spirometry was performed 10 minute pre-dose (window of 5 to 25 minutes pre-dose), followed by usual maintenance therapy and first dose of study medication. PFTs were repeated at 30 and 60 minutes (± 5 minutes) and 2 and 3 hours (± 10 minutes) post-dose. At the following study visits (Visits 3, 4, and 6), PFTs were performed according within ± 30 minutes from the start of the tests on Visit 2 (see Appendix, Table 32).

Interviewer-Administered Asthma Control Questionnaire (ACQ-IA)

The interviewer-administered version of the ACQ was developed for children < 11 years of age and has been validated in studies of children 6 years and older.[5] The ACQ-IA, has 6 patient interviewer-administered questions for the time period of the last week prior to the visit and one question concerning pre-bronchodilator FEV_1 (see Appendix, Figure 12). Each question is on a 7-point scale, and all questions are weighted equally. The score is the mean of responses to all 7 questions. The ACQ-IA was administered

[5] Juniper EF, Gruffydd-Jones K, Ward S, Svensson K. Eur Respir J. 2010; 36: 1410-1416

at Visit 1 and repeated at Visit 2 as part of eligibility screening and administered at every visit during the treatment period (Visits 3, 4, and 6).

Standardized Pediatric Asthma Quality of Life Questionnaire (PAQLQ(S))
The PAQLQ(S) is an interviewer administered version of the AQLQ(S) for pediatric patients; during the interview, parents were not to be present. The PAQLQ (Appendix, Figure 13) has 23 questions in 3 domains (symptoms, activity limitation, and emotional function). Its recall period is the previous week, and children were asked to respond to each of the 23 questions on a 7-point scale (7=not bothered at all, 1=extremely bothered). The standardized version has the same generic activity questions for all patients rather than patient-specific questions in the activity domain. The overall PAQLQ score is the mean of all 23 responses and the individual domain scores are the means of the items in those domains.

Electronic peak flow meter with electronic diary (Asthma Monitor AM3)
The Asthma Monitor AM3 is a combined electronic peak flow meter (PEF and FEV_1) and electronic diary in one device. Patients/caregivers received the AM3 at Visit 1 and were instructed to use the device twice daily to complete the questions and measure PEF/FEV_1. Morning and evening recordings were to be performed at approximately the same time of the day – between 5 a.m. and 9 a.m. and between 4 p.m. and 7 p.m. The questions captured asthma symptoms (nighttime awakenings and daytime symptoms) as well as study medication compliance and rescue medication use.

Asthma exacerbations
Worsening of asthma symptoms and subsequent changes to required asthma medication were captured in the AM3 device and on a paper patient diary card which was entered in the eCRF at study visits. For the purposes of this trial, an asthma exacerbation was defined by the Applicant as:

- 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 for at least 2 consecutive days

AND/OR

- A decrease of patient's best morning PEF of ≥ 30% from the patient's mean morning PEF for at least 2 consecutive days. During the treatment period, the patient's 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.

A severe asthma exacerbation was defined as any asthma exacerbation requiring initiation of systemic corticosteroids for at least 3 days. Symptomatic asthma exacerbations excluded those that were only triggered by a decrease in PEF (i.e., an asymptomatic drop in PEF that may have been detected by the AM3).

The onset of an asthma exacerbation was considered the onset of the first worsened symptom, and the end of an exacerbation was defined by the investigator. Courses of corticosteroids separated by one week or more were treated as separate exacerbations.

Safety Variables/Endpoints

Safety variables included adverse events, hepatic injury as an adverse event of special interest, vital signs, ECG, physical exam, and laboratory results which were assessed according to the schedule in Table 5.

Table 5. Schedule of Assessments (Study 445)

Trial Periods	Screening		Treatment									Follow-up
Visit[1]	0	1	2	☎	3	☎	4	☎	5	☎	6/ EoT[3]	7
Week	-	-4	0	6	12	18	24	30	36	42	48	51
Day[2]	-	-28 ± 4	1	42 ± 4	84 ± 4	126 ± 4	168 ± 4	210 ± 4	252 ± 4	294 ± 4	336 ± 4	V6+ 21 +7
Informed consent/assent[4]	X											
Instruct patient on wash-out / Restriction	X	X	X	X	X	X	X	X	X	X		
Demographics		X										
Med. History/Baseline conditions[5]		X										
Physical examination		X					X				X	X
12-lead ECG		X									X	
Laboratory testing[6]		X					X				X	
Urine pregnancy test[7]		X	X		X		X		X		X	X
Review of In / Exclusion Criteria	X[8]	X	X									
Blood sample pharmacogenomics[9]											X	
Dispense rescue medication[10]	X	X	X		X		X		X		X	
Collect rescue medication[10]		X	X		X		X		X		X	X
Respimat® training[22]		X	X		X		X		X			
Randomization			X									
Dispense trial medication			X		X		X		X			
Administer trial medication in clinic[11]			X		X		X		X		X[3]	
Collect trial medication					X		X		X		X	
Drug accountability and compliance check[10]	X	X	X		X		X		X		X	X
Training eDiary / PEF-meter[23]		X	X		X		X		X			
Issue eDiary / PEF-meter		X										

Trial Periods	Screening		Treatment									Follow-up
Visit[1]	0	1	2	☎	3	☎	4	☎	5	☎	6/ EoT[3]	7
Week		-4	0	6	12	18	24	30	36	42	48	51
Day[2]		-28 ± 4	1	42 ± 4	84 ± 4	126 ± 4	168 ± 4	210 ± 4	252 ± 4	294 ± 4	336 ± 4	V6+ 21 +7
Download, Review eDiary / PEF-meter[12]			X		X		X		X		X	
Collect, Close eDiary / PEF-meter											X	
Issue paper diary cards[13]		X	X		X		X		X			
Collect, Review paper diary cards[13]			X		X		X		X		X	
ACQ-IA[14]		X[15]	X[15]		X		X				X[3]	
PAQLQ(S)[14]			X				X				X[3]	
Review exacerbations		X	X	X	X	X	X	X	X	X	X	X
Medication wash out check		X	X	X	X	X	X	X	X	X	X	
Pulmonary function tests		X[16]	X[17,18]		X[18]		X[18]				X[18,3]	
Vital signs (seated)		X	X[19]		X[19]		X[19]				X[19]	X[20]
Height		X	X		X		X				X[20]	
Adverse events		X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy		X	X	X	X	X	X	X	X	X	X	X
Vital status												X[21]
Trial medication termination											X	
Trial completion												X

1 Visit 0, Visit 5 and Visit 7 may be conducted in the morning or in the afternoon/evening. Visits 1 to 4 and Visit 6 will always end in the afternoon/evening in order to allowed PFTs during afternoon/evening hours (for exact timing please refer to chart below).

2 The interval between Visit 0 and Visit 1 may be between 0 and 28 days depending on medication wash-out requirements and restrictions. The interval between Visit 1 and Visit 2 may be 28 days ± 4. Each Respimat® inhaler contains drug supply for 30 days, which are to be taken into account regarding visit flexibility after randomisation.

3 An End of Treatment visit (EoT) should be completed as soon as possible after last intake of study medication by all patients who took at least one dose of trial medication and prematurely discontinued intake of trial medication. Administration of trial medication in clinic, ACQ-IA and PAQLQ (S) are not required for prematurely discontinued patients attending an EoT (see Section 6.2.2). PFT until 3 hours post-dose is not required: a single pulmonary function test (whenever feasible) will be performed.

4 Prior to any other trial procedures, which includes medication wash-out and restrictions (see Section 4.2.2), the investigator must obtain the informed consent from the parent(s) (or legal guardian) and the informed assent from the patient according to ICH GCP guidelines and local legislation (see Section 8.1). A separate consent/assent for pharmacogenomic sampling should be signed prior to sampling of pharmacogenomic evaluation.

5 Including asthma background characteristics.
6 Haematology and blood chemistry (see Appendix 10.10).
7 Urine pregnancy testing only for all postmenarchal girls.
8 A preliminary check of in-/exclusion criteria is recommended at Visit 0 to avoid unnecessary wash-out procedures in non-eligible patients.
9 Blood sample for pharmacogenomics will be drawn from all enrolled patients that gave a separate informed assent (and whose parent(s) (or legal guardian) gave a separate informed consent) for pharmacogenomic evaluation. Participation in the pharmacogenomic evaluation is not a pre-requisite for participation in the trial. The blood sample will be collected at Visit 6/EoT in conjunction with laboratory testing (to avoid extra venipuncture).
10 Rescue medication will be dispensed at Visit 0; at Visits 1 to 6 new rescue medication may be dispensed, if needed, used rescue medication will be collected and drug accountability will be completed. At Visit 7 all used and unused rescue medication will be collected and drug accountability will be completed. Drug accountability will be completed for rescue medication at Visits 0-7, and for trial medication at Visits 2-6. Compliance check will be completed only for trial medication at Visits 3-6 (see Section 4.3).
11 Trial medication and patient's usual maintenance therapy will be administered in fixed sequence: 1. iCS (if regular posology); 2. other controller medications if any; 3. trial medication from Respimat®. Patient's usual maintenance therapy should be administered without change in posology (b.i.d./q.d.; a.m./p.m.), i.e. as previously prescribed by patient's treating physician. Trial medication is administered at Visit 5 only if this visit is performed in the afternoon/evening.
12 e-Diary/PEF-meter compliance check (see Section 5.1.2). At Visits 2- 5 the eDiary/PEF-meter battery will be replaced.
13 A paper diary card will be dispensed at Visit 1; at Visits 2 to 5 a paper diary card may be dispensed, if needed, and completed diary card will be collected. At Visit 6/EoT the paper diary card will be collected.
14 First ACQ-IA, then PAQLQ(S) (only at Visits 2, 4 and 6/EoT) will be administered at the beginning of the visit and should precede any discussion with a health professional.
15 ACQ-IA at screening will be used for assessment of degree of asthma control. If the patient is not eligible due to the predefined score at Visit 1, the patient should not be further evaluated. If the patient is not eligible due to the predefined score at Visit 2, the patient's Visit 2 can be repeated once for further assessment (see Section 6.1).
16 10 min pre- and 15 to 30 min post bronchodilator (200µg salbutamol/albuterol) (see Appendix 10.3).
17 Pre-bronchodilator FEV_1 at Visit 1 and pre-dose FEV_1 at Visit 2 must be within ± 30% variation prior to randomization based on absolute FEV_1 values. If the variation of FEV_1 in the screening period exceeds ± 30%, the patient's Visit 2 can be repeated once for further assessment (see Section 6.1).
18 10 minutes prior to trial drug administration (pre-dose) at Visits 2, 3, 4, 6 and until 3 hours post-dose (for exact timing please refer to chart below) at Visits 2, 4 and 6 only.
19 Measured immediately before PFT, in conjunction with pre-dose pulmonary function testing at Visits 2, 3, 4, 6 and until 3 hours post-dose at Visits 2, 4 and 6.
20 In conjunction with physical examination.
21 Vital status information has to be collected for all patients who discontinued prematurely on the originally planned date of Visit 7.
22 Training with device contains placebo, video suitable for this age group and standard instructions for use will be administered at Visit 1; instructions will be repeated at Visits 2 to 5 and the correct inhalation technique will be observed by study personnel.
23 Training on eDiary/PEF-meter will be administered at Visits 1 and 2. At Visits 3 to 5 the eDiary/PEF-meter will be used under supervision of study personnel and training will be repeated.

Source: Clinical Trial Protocol 205.445, Flow Chart, p5

Efficacy Endpoints

The primary efficacy endpoint was the peak FEV_1 response within 3 hours post dosing (FEV_1 $peak_{0-3h}$ response) determined at the end of the 24-week treatment period. Peak FEV_1 was defined as the highest FEV_1 reading observed within 3 hours after administration of the evening dose of each randomized treatment. Peak FEV_1 response was defined as the change from baseline in peak FEV_1. Baseline was defined as the pre-treatment FEV_1 measured at Visit 2 in the evening 10 minutes prior to the evening dose of the patient's usual asthma medication and first dose of trial medication.

The key secondary endpoint was the trough forced expiratory volume in one second (trough FEV_1) response determined at the end of the 24-week treatment period. Trough FEV_1 was defined as the FEV_1 measured in the evening at the end of the dosing interval (24 hours post drug administration), 10 minutes prior to the evening dose of the patient's usual asthma medication, and daily dose of trial medication. Trough FEV_1 response was defined as the change from baseline in trough FEV_1.

Secondary efficacy endpoints included:

- Trough FEV_1 response at the end of the 48-week treatment period
- Peak forced vital capacity (FVC) response within 3 hours post dosing (FVC $peak_{0-3h}$) at 24 and 48 weeks
- Trough FVC response at 24 and 48 weeks

- FEV_1 ($AUC_{0\text{-}3h}$) and FVC ($AUC_{0\text{-}3h}$) response at 24 weeks. ($AUC_{0\text{-}3h}$ was calculated as area under the curve from zero to 3 hours using the trapezoidal rule divided by the observation time (3 hours) and reported in liters. Trough values were assigned to time zero.)
- Individual in-clinic FEV_1 and FVC response measurements at 24 weeks
- Asthma control as assessed by ACQ-IA at 24 and 48 weeks
- Number of responders as assessed by the ACQ-IA at 24 and 48 weeks with responders defined as those with improvement of ≥ 0.5
- Quality of life as assessed by PAQLQ(S) at 24 and 48 weeks
- Rescue medication use at 24 and 48 weeks, calculated as mean number of inhalations/puffs used per day during weeks 24 and 48
- PEF and FEV_1 a.m./p.m. response, defined as change from baseline in mean weekly pre-dose a.m. and p.m. PEF and FEV_1 measured by patients at home using the AM3 device at weeks 24 and 48 (baseline defined as the last week prior to randomization)
- PEF variability response at week 24 and 48, defined as the absolute difference between morning and evening PEF values divided by the mean of these two values
- Asthma symptoms as assessed by the patient's electronic diary at weeks 24 and 48

Further efficacy endpoints included:

- Additional PFT endpoints
    - Individual $FEF_{25\text{-}75}$ response at each time point and visit during the 48-week treatment period
    - Individual in-clinic FEV_1 and FVC response at each time point during the 48-week treatment period
    - FEV_1 ($AUC_{0\text{-}3h}$) and FVC ($AUC_{0\text{-}3h}$) response at the end of the 48-week treatment period
    - FEV_1 $peak_{0\text{-}3}$ and trough FEV_1 expressed as FEV_1 percent predicted after 24 and 48 weeks
- Daily rescue medication use evaluated as weekly means during the 48 week treatment period
- Weekly PEF and FEV_1 a.m./p.m. response and PEF variability response during the 48 week treatment period
- Asthma symptom free days during the 48 week treatment period
- Time to first severe asthma exacerbation
- Time to first asthma exacerbation
- Time to first symptomatic asthma exacerbation
- ACQ-IA6 at 24 and 48 weeks
- Number of ACQ-IA6 responders at 24 and 48 weeks

Statistical Analyses

Efficacy and safety analyses were based on all randomized patients who received at least one dose of trial medication (Treated Set, TS); this set of patients was considered the Full Analysis Set (FAS).

The primary endpoint of FEV_1 $peak_{0\text{-}3h}$ response after 24 weeks of treatment was analyzed using a restricted maximum likelihood (REML)-based Mixed Model Repeated Measures (MMRM). The model included the fixed categorical effects of treatment, country, visit, and treatment-by-visit interaction as well as continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as a random effect. A spatial power structure for unequally spaced visits was used to model the within-patient errors. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. The primary comparison was difference between treatment groups at week 24. For sensitivity analysis of the primary endpoint, the analysis of covariance model (ANCOVA) with last observation carried forward (LOCF) imputation for missing data was used for the respective time points.

For all clinical spirometry and vital sign endpoints, the pre-treatment value measured at the randomization visit (Visit 2) 10 minutes prior to the first dose of study drug was defined as baseline. Baseline for endpoints derived from the AM3 device was defined as the average of the 7 days immediately preceding the randomization visit. Baseline for questionnaire-based endpoints was defined as the value obtained prior to the first intake of study medication.

To control for Type I error, analyses were conducted in a stepwise manner:

- First: efficacy was established on the primary endpoint of TioR5 over placebo
- Second: efficacy was established on the primary endpoint of TioR2.5 over placebo
- Third: efficacy was established on the key secondary endpoint of TioR5 over placebo
- Fourth: efficacy was established on the key secondary endpoint of TioR2.5 over placebo

Hypothesis testing was performed at the one-sided alpha level of 0.025 (i.e. at the 2-sided alpha level of 0.05 if the treatment was in favor of tiotropium). Significance was declared if results were significant at the 0.05 2-sided level and if the effect was in favor of tiotropium. Subgroup analyses were performed for the primary and key secondary endpoints and PEF endpoints by age group (6-8 years vs 9-11 years).

All other PFT and AM3 endpoints were analyzed using the MMRM described for the analysis of the primary endpoint. The ACQ-IA-6, ACQ-IA total score, and PAQLQ(S) were analyzed as absolute values using MMRM as described for the primary endpoint analysis with the exception that first-order autoregressive structure instead of spatial power structure was used to model within-patient errors for the PAQLQ(S) analysis. Responder analyses for ACQ-IA total score, ACQ-IA-6, and PAQLQ(S) total score were

performed using a minimal important difference of 0.5 for each score. All endpoints related to asthma exacerbations were analyzed using the Cox's proportional hazards regression model with treatment fitted as an effect. The confidence interval was calculated using the method by Brookmeyer and Cowley based on the log-log transformation. Safety analyses were descriptive in nature.

Study Number	**205.446**
Title	A randomized, double-blind, placebo-controlled, parallel-group trial to evaluate efficacy and safety of tiotropium inhalation solution (2.5 µg and 5 µg) delivered via Respimat inhaler once daily in the evening over 12 weeks in children (6 to 11 years old) with severe persistent asthma
Study dates	July 24, 2012 to May 18, 2015
Study report	September 29, 2015
Sites	92 sites in 17 countries

Amendments
Global amendments #1 and #2, dated February 25, 2013 and February 12, 2015, respectively, provided similar revisions as those described for Study 445.

Objectives
The primary objective of the trial is to demonstrate superiority of tiotropium (5 µg and possible 2.5 µg once daily in the evening) over placebo with regard to the primary pulmonary function endpoint after 12 weeks of treatment. Secondary objectives are to evaluate efficacy of tiotropium with regard to other efficacy endpoints, and to evaluate the safety of tiotropium, compared to placebo, as add-on controller therapy on top of usual care in this patient population.

Study Design
This was a randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of two doses of tiotropium inhalation solution delivered via the Respimat inhaler once daily in the evening over 12 weeks in children 6 to 11 years of age with severe persistent asthma.

Patient Population
A total of 375 patients were to be randomized into the study. Individual study sites were expected to enroll 3-4 patients on average. Eligibility criteria were the same as for Study 445 with the exception of asthma severity characterized by background maintenance therapy as outlined below:

Inclusion Criterion

1. Maintenance treatment with an ICS at stable high dose in combination with ≥ 1 controller medication (e.g., LABA or leukotriene modifier) or stable medium dose in combination with ≥ 2 controller medications (e.g., LABA and/or leukotriene modifier and/or sustained release theophylline) for at least 4 weeks before Visit 1. High and medium doses of ICS were defined according to GINA guidelines as shown in Table 6.

Table 6. Classification of Medium and High Dose ICS (Study 446)

Drug Name	Medium daily dose (µg)	High daily dose (µg)
Beclomethasone dipropriate	≥ 200 to ≤ 400	> 400
Budesonide	≥ 200 to ≤ 400	> 400
Budesonide-Neb	≥500 to ≤ 1000	> 1000
Ciclesonide	≥160 to ≤ 320	> 320
Flunisolide	≥ 750 to ≤ 1250	> 1250
Fluticasone propionate	≥ 200 to ≤ 500	> 500
Mometasone furoate	≥ 200 ≤ 400	> 400
Triamcinolone acetonide	≥ 800 ≤ 1200	> 1200
Source: Clinical Trial Protocol 205.446, Appendix 10.3, Table 10.3:1, p110		

Concomitant Medications

The following table lists medications that were allowed, prohibited, or required prior to enrollment and during the study.

Table 7. Required, Permitted, and Restricted Concomitant Medications (Study 446)

Drug Class	Sub-class	Prior to study	Study Period		
			Screening Period	Treatment Period	Follow-up Period
Corticosteroids	Inhaled corticosteroids	REQUIRED Stable within 4 weeks prior to Visit 1	REQUIRED	REQUIRED	REQUIRED
	Systemic (e.g. oral or i.v.) corticosteroids	NOT permitted within 4 weeks prior to Visit 1	NOT permitted (except for treatment of asthma exacerbation)	NOT permitted (except for treatment of asthma exacerbation)	NOT permitted (except for treatment of asthma exacerbation)
	Topical (e.g. intranasal) corticosteroids (e.g. Nasonex®)	Permitted	Permitted	Permitted	Permitted
Beta-adrenergics	Inhaled short-acting β_2-agonists	Permitted	Permitted only rescue medication provided[1]	Permitted only rescue medication provided[1]	Permitted
	Inhaled long-acting β_2-agonists	Permitted	Permitted[1]	Permitted[1]	Permitted
	Systemic (e.g. oral or i.v. or s.c.) β_2-agonists (cave: this includes Spasmo Mucosolvan®)	NOT permitted within 4 weeks prior to Visit 1	NOT permitted (except for treatment of asthma exacerbation)	NOT permitted (except for treatment of asthma exacerbation)	NOT permitted (except for treatment of asthma exacerbation)
Beta blockers	Beta blockers (oral or i.v.) (e.g. Inderal®) (except topical eye medications)	NOT permitted within 4 weeks prior to Visit 1	NOT permitted	NOT permitted	NOT permitted

Drug Class	Sub-class	Prior to study	Study Period		
			Screening Period	Treatment Period	Follow-up Period
Anticholinergics	Inhaled short-acting anticholinergics (inhalation aerosol and nasal spray) (e.g. Atrovent®)	NOT permitted within 2 weeks prior to Visit 1	NOT permitted (except for treatment of asthma exacerbation)	NOT permitted (except for treatment of asthma exacerbation)	Permitted
	Inhaled long-acting anticholinergics (e.g. Spiriva®)	NOT permitted within 4 weeks prior to Visit 1	NOT permitted	Study medication	NOT permitted
	Systemic (s.c., i.v. or oral) anticholinergics, e.g. spasmolytics, muscle relaxants	NOT permitted within 4 weeks prior to Visit 1	NOT permitted	NOT permitted	NOT permitted
Leukotriene modifiers	Leukotriene modifiers (e.g. montelukast-Singulair®)	Permitted Stable within 4 weeks prior to Visit 1	Permitted	Permitted	Permitted
Methylxanthines	Short-acting theophyllines (e.g. Theolair®)	NOT permitted within 2 weeks prior to Visit 1	NOT permitted (except for treatment of asthma exacerbation)	NOT permitted (except for treatment of asthma exacerbation)	NOT permitted (except for treatment of asthma exacerbation)
	Long-acting theophyllines (e.g. Theolair® retard)	Permitted Stable within 4 weeks prior to Visit 1	Permitted[l]	Permitted[l]	Permitted

Drug Class	Sub-class	Prior to study	Study Period		
			Screening Period	Treatment Period	Follow-up Period
Combination medications	Combination iCS/ long-acting β_2-agonist (e.g. Advair®/ Seretide®, Symbicort®)	Permitted Stable within 4 weeks prior to Visit 1	Permitted[l]	Permitted[l]	Permitted
	Combination iCS/ short-acting β_2-agonist (e.g. Butasol®)	Permitted	NOT permitted Patient should be switched to the inhaled steroid mono-product, without changing the steroid dose, at least 8 hours prior to Visit 1	NOT permitted	Permitted
	Combination short-acting anticholinergic/ short-acting β_2-agonist (e.g. Berodual®, Combivent®, Duovent®)	NOT permitted within 2 weeks prior to Visit 1	NOT permitted	NOT permitted	Permitted

Drug Class	Sub-class	Prior to study	Study Period		
			Screening Period	Treatment Period	Follow-up Period
Miscellaneous	Anti-IgE treatment (e.g. omalizumab - Xolair®)	Permitted Stable within 6 months prior to Visit 1	Permitted	Permitted	Permitted
	Mucolytics (not containing bronchodilators)	Permitted	Permitted	Permitted	Permitted
	Cromones (e.g. sodium cromoglycate, nedocromil sodium)	Permitted Stable within 4 weeks prior to Visit 1	Permitted	Permitted	Permitted
	Antihistamines	Permitted	Permitted	Permitted	Permitted
	'Experimental', non-approved asthma medications (e.g. TNF-alpha blockers, as defined in Section 3.3.3)	NOT permitted within 4 weeks prior to Visit 1	NOT permitted	NOT permitted	NOT permitted
	Other investigational drugs	NOT permitted within 4 weeks or six half lives (whichever is greater) prior to Visit 1	NOT permitted	NOT permitted	NOT permitted

Source: Clinical Trial Protocol 205.446, Table 4.2.2.1:1, p52

Study Treatments

Study treatments and timing of administration were the same as in Study 445.

Efficacy Assessments and Endpoints

Efficacy variables were the same as in Study 445 and were assessed using the same methods with the exception of the time point of interest being 12 weeks rather than 24 or 48 weeks given the shorter duration of this study. Additionally, the PAQLQ(S) was not performed in this study.

Safety Variables and Endpoints

Safety assessments and endpoints were identical to those in Study 445.

A schedule of efficacy and safety assessments is provided in the table below.

Table 8. Schedule of Assessments: Study 446

Trial Periods	Screening		Treatment				Follow-up
Visit[1]	0	1	2	3	4	5 / EoT[3]	6
Week	-	-4	0	4	8	12	
Day Time window for visits (days)[2]	-	-28 ± 4	1	29 ± 2	57 ± 2	85 ± 2	V5+21 +7
Informed consent/assent[4]	X						
Instruct patient on wash-out/restrictions	X	X	X	X	X		
Demographics		X					
Medical history/baseline conditions[5]		X					
Physical examination		X				X	X
12-lead ECG		X				X	
Laboratory testing[6]		X				X	
Urine pregnancy testing[7]		X	X	X	X	X	X
Review of inclusion/exclusion criteria	X[8]	X	X				
Blood sample for pharmacogenomics[9]						X	
Dispense rescue medication[10]	X	X	X	X	X	X	
Collect rescue medication[10]		X	X	X	X	X	X
Respimat® training[11]		X	X	X	X		
Randomisation			X				
Dispense trial medication			X	X	X		
Administer trial medication in clinic[12]			X	X	X	X[3]	
Collect trial medication				X	X	X	
Drug accountability and compliance check[13]	X	X	X	X	X	X	X
Training eDiary/PEF-meter[14]		X	X	X	X		
Issue eDiary/PEF-meter		X					
Download, Review eDiary/PEF-meter[15]			X	X	X	X	
Collect, Close eDiary/PEF-meter						X	
Issue paper diary card[16]		X	X	X	X		
Collect, Review paper diary card[16]			X	X	X	X	
ACQ-IA[17]		X[18]	X[18]	X	X	X[3]	
Review asthma exacerbation		X	X	X	X	X	X
Medication wash-out check		X	X	X	X	X	
Pulmonary function testing		X[19]	X[20,21]	X[21]	X[21]	X[3,21]	
Vital signs (seated)		X	X[22]	X[22]	X[22]	X[22]	X[23]
Height		X	X	X	X	X[23]	
Adverse events		X	X	X	X	X	X
Concomitant therapy		X	X	X	X	X	X
Termination of trial medication						X	
Trial Completion							X

1 Visit 0 and Visit 6 may be conducted in the morning, or in the afternoon/evening. Visits 1 to 5 will always end in the afternoon/evening, in order to allow PFTs during afternoon/evening hours (for exact timing please refer to chart below).
2 The interval between Visit 0 and Visit 1 may be between 0 and 28 days depending on medication wash-out requirements and restrictions. The interval between Visit 1 and Visit 2 should be 28 days ± 4 days. Each Respimat® inhaler contains drug supply for 30 days, which are to be taken into account regarding visit flexibility after randomisation.
3 An End of Treatment visit (EoT) should be completed as soon as possible after last intake of study medication by all patients who took at least one dose of trial medication and prematurely discontinued intake of trial medication. Administration of trial medication in clinic and ACQ-IA are not required for prematurely discontinued patients attending an EoT (see Section 6.2.2). PFT until 3 hours post-dose is not required: a single pulmonary function test (whenever feasible) will be performed.
4 Prior to any other trial procedures, which includes medication wash-out and restrictions (see Section 4.2.2), the investigator must obtain the informed consent from the parent(s) (or legal guardian) and informed assent from the patient according to ICH GCP guidelines and local legislation (see Section 8.1). A separate consent/assent for pharmacogenomic sampling should be signed prior to sampling for pharmacogenomic evaluation.
5 Including asthma background characteristics.
6 Haematology and blood chemistry (See Appendix 10.9).
7 Urine pregnancy testing only for all postmenarchal girls.
8 A preliminary check of in-/exclusion criteria is recommended at Visit 0 to avoid unnecessary wash-out procedures in non-eligible patients.
9 Blood sample for pharmacogenomics will be drawn from all enrolled patients that gave a separate informed assent (and whose parent(s) or legal guardian gave a separate informed consent) for pharmacogenomic evaluation. Participation in the pharmacogenomic evaluation is not a pre-requisite for participation in the trial. The blood sample will be collected at Visit 5/EoT in conjunction with laboratory testing (to avoid extra venipuncture).
10 Rescue medication will be dispensed at Visit 0; at Visits 1 to 5 new rescue medication may be dispensed, if needed, used rescue medication will be collected and drug accountability will be completed. At Visit 6 all used and unused rescue medication will be collected and drug accountability will be completed.
11 Training with device containing placebo, video suitable for this age group and standard instructions for use will be administered at Visit 1; instructions will be repeated at Visits 2 to 4, and the correct inhalation technique will be observed by study personnel.
12 Trial medication and patient's usual maintenance therapy will be administered in fixed sequence: 1. iCS (if regular posology); 2. other controller medications (if any); 3. trial medication from Respimat®. Patient's usual maintenance therapy should be administered without change in posology (b.i.d./q.d.; a.m./p.m.), i.e. as previously prescribed by patient's treating physician.
13 Drug accountability will be completed for rescue medication at Visits 0 to 6, and for trial medication at Visits 2 to 5. Compliance check will be completed only for trial medication at Visits 3 to 5 (see Section 4.3).
14 Training on eDiary/PEF-meter will be administered at Visit 1 and Visit 2. At Visit 3 and Visit 4 the eDiary/PEF-meter will be used under supervision of the study personnel, and training will be repeated.
15 e-Diary/PEF-meter compliance check (see Section 5.1.2.).
16 A paper diary card will be dispensed at Visit 1; at Visits 2 to 4 a paper diary card may be dispensed, if needed, and completed diary card will be collected. At Visit 5/EoT the paper diary card will be collected.
17 The ACQ-IA will be administered at the beginning of the visit and should precede any discussion with a health professional.
18 ACQ-IA at screening will be used for assessment of degree of asthma control. If the patient is not eligible due to the predefined score at Visit 1, the patient should not be further evaluated. If the patient is not eligible due to the predefined score at Visit 2, the patient's Visit 2 can be repeated once for further assessment (see Section 6.1).
19 10 minutes pre- and 15 to 30 minutes post-bronchodilator PFT after inhalation of 200 µg salbutamol/albuterol (see Appendix 10.3).
20 Pre-bronchodilator FEV_1 at Visit 1 and pre-dose FEV_1 at Visit 2 must be within ± 30% variation prior to randomisation based on absolute FEV_1 values. If the variation of FEV_1 in the screening period exceeds ± 30%, the patient's Visit 2 can be repeated once for further assessment (see Section 6.1).
21 10 minutes prior to trial drug administration at Visits 2, 3, 4 and 5 (pre-dose), and until 3 hours post-dose at Visit 2 and Visit 5 only (for exact timing please refer to chart below).
22 Measured immediately before PFT, in conjunction with pre-dose pulmonary function testing at Visits 2, 3, 4 and 5 and until 3 hours post-dose at Visit 2 and Visit 5.
23 In conjunction with physical examination.

Source: Clinical Trial Protocol 205.446, Flow Chart, p5

Statistical Analyses

Endpoints were analyzed at the 12 week time point using the same statistical methods as described for Study 445.

Study Number	205.443
Title	A phase II/III randomized, double-blind, placebo-controlled, parallel group trial to evaluate safety and efficacy of tiotropium inhalation solution (2.5 and 5 µg) administered once daily in the afternoon via Respimat Inhaler for 12 weeks in patients 1 to 5 year old with persistent asthma
Study dates	July 26, 2012 to December 4, 2014
Study report	May 21, 2015
Sites	32 sites in 11 countries

Amendments

Global protocol amendment #1, dated December 5, 2012, added impulse oscillometry as an alternative efficacy assessment; added ALT, AST, and GGT to laboratory test parameters; specified that withdrawn patients will not be replaced; and allowed use of

transdermal beta-2 agonists which are approved and commonly used in Asian countries. Global amendment #2, dated May 7, 2013, specified recruitment of at least 30 patients aged 1 to 2 years; did not require serum IgE testing at Visit 1 if recent (within last 6 months) results were available; and allowed for a temporary interruption in completing the pediatric asthma care giver diary if Visit 2 was postponed due to asthma exacerbation or respiratory infection.

Objectives

The primary objective was to evaluate the safety and efficacy of two doses of tiotropium inhalation solution delivered via the Respimat inhaler once daily in the afternoon in patients 1 to 5 years old with moderate and severe persistent asthma on top of adequate ICS treatment. Treatment comparisons were exploratory and no formal hypotheses testing was performed.

Study Design

This was a randomized, double-blind, placebo-controlled, parallel group study designed to evaluate the safety and efficacy of tiotropium inhalation solution 2.5 and 5 µg administered once daily in the afternoon via the Respimat Inhaler ± a spacer for 12 weeks in patients 1 to 5 years old with moderate and severe persistent asthma.

After providing Informed Consent and completing an initial screening visit, patients entered a 2-week screening period to ensure clinical stability. Patients who continued to meet all eligibility criteria were randomized at Visit 2 to one of three treatment groups for a 12-week treatment period. Follow up clinic visits were scheduled for Weeks 3, 8, 12, and 15 with phone contact occurring in between visits. PFTs were performed in 5 year olds who were capable of performing acceptable and reproducible results.

Patient Population

A total of 102 patients were to be randomized in the trial with at least 30 patients in the 1 to 2 year old age range.

Key Inclusion Criteria

1. Males or females between 1 and 5 years of age (up to 1 day prior to their 6th birthday at Visit 1)
2. Physician documented history of persistent asthma symptoms for at least 6 months, requiring ICS maintenance therapy for control
3. For patients 5 years of age and capable of performing PFTs, pre-bronchodilator FEV1 ≤ 90% predicted
4. Maintenance treatment with ICS at a stable dose either as monotherapy or in combination with another controller medication for at least 4 weeks before Visit 1
5. Symptomatic/partially controlled as defined in Table 9 in the week prior to Visits 1 and 2.
6. Ability to inhale from the Respimat inhaler with or without spacer

Table 9. GINA definition of partly controlled asthma: Study 443

Characteristic	Partly controlled (any measure present in the week prior to the visit)
Daytime symptoms: wheezing, cough, difficult breathing	More than twice/week (typically for short periods on the order of minutes and rapidly relieved by use of a rapid-acting bronchodilator)
Limitations of activities	Any (may cough, wheeze, or have difficulty breathing during exercise, vigorous play, or laughing)
Nocturnal symptoms/awakenings	Any (typically coughs during sleep or wakes with cough, wheezing, and/or difficult breathing)
Need for reliever/rescue treatment	>2 days/week

Key Exclusion Criteria

Same as in Study 445 with the addition of the following:

1. Alternative causes (other than asthma) that can lead to respiratory symptoms of wheeze, cough and shortness of breath, such as, but not limited to, transient viral infection, primary immunodeficiency, congenital heart disease, parasitic disease, vocal cord dysfunction and foreign body aspiration

Concomitant Medications

The following table lists medications that were allowed and prohibited prior to and during the study.

Table 10. Required, permitted, and restricted medications: Study 443

Drug Class	Sub-class	Study Period		
		Screening Period	Treatment Period	Follow up Period
Corticosteroids	Inhaled corticosteroids	REQUIRED	REQUIRED	REQUIRED
	Systemic (e.g. oral or i.v.) corticosteroids	not permitted[1] (except for treatment of asthma exacerbation)	not permitted	not permitted
	Topical (e.g.intranasal) corticosteroids (e.g. Nasonex®)	permitted	permitted	permitted
Beta-adrenergics	Inhaled short-acting β_2-agonists	rescue	rescue	permitted
	Inhaled long-acting β_2-agonists	permitted[4]	permitted	permitted
	Transdermal long-acting β_2-agonists (e.g. patch)	permitted[4]	permitted	permitted
	Systemic (e.g. oral or i.v. or s.c.) β_2-agonists (cave: this includes Spasmo Mucosolvan®)	not permitted[1] (except for treatment of asthma exacerbation)	not permitted	not permitted
Beta blockers	Beta blockers (oral or i.v.) (e.g. Inderal®) (except topical eye medications)	not permitted[1]	not permitted	not permitted
Anticholinergics	Inhaled short-acting anticholinergics (inhalation aerosol and nasal spray) (e.g. Atrovent®)	not permitted[2] (except for treatment of asthma exacerbation)	not permitted	permitted
	Inhaled long-acting anticholinergics (e.g. Spiriva®)	not permitted[1]	Study medication	not permitted
	Systemic (s.c., i.v. or oral) anticholinergics, e.g. spasmolytics, muscle relaxants	not permitted[1]	not permitted	not permitted
Combination medications	Combination ICS/ long-acting β_2-agonist (e.g. Advair®/ Seretide®, Symbicort®, Foster®, Dulera®)	not permitted[7]	not permitted	permitted
	Combination ICS/ short-acting β_2-agonist (e.g. Butasol®)	not permitted[6]	not permitted	permitted
	Combination short-acting anticholinergic/ short-acting β_2-agonist (e.g. Berodual®, Combivent®, Duovent®)	not permitted[2]	not permitted	permitted
Methylxanthines	Short-acting theophillines (e.g. Theolair®)	not permitted[2] (except for treatment of asthma exacerbation)	not permitted	not permitted
	Long-acting theophillines (e.g. Theolair® retard)	not permitted[1]	not permitted	not permitted
Miscellaneous	Other investigational drugs	not permitted[5]	not permitted	not permitted
	Leucotriene modifiers (e.g. montelukast Singulair®)	permitted[4]	permitted	permitted
	Anti-IgE treatment (e.g. omalizumab, Xolair®)	not permitted[5]	not permitted	not permitted
	Cromones (e.g. sodium cromoglycate, nedocromil sodium)	permitted[4]	permitted	permitted
	Antihistamines	permitted	permitted	permitted
	Mucolytics (not containing bronchodilators)	permitted	permitted	permitted
	Experimental, non-approved asthma medications (e.g. TNFα-blockers)[8]	not permitted[1]	not permitted	not permitted
	Sedatives, tranquillizers (e.g. chloral hydrate , midazolam)	not permitted	not permitted	not permitted

1. Not permitted within 4 weeks prior to Visit 1.
2. Not permitted within 2 weeks prior to Visit 1.
3. Not permitted within 6 months prior to Visit 1.
4. To be stabilised for at least 4 weeks prior to the trial and stable throughout the trial.
5. Washout of at least one month or six half lives (whichever is greater).
6. To be switched to the inhaled steroid mono-product (without changing the steroid dose or substance) at least 8 hours prior to Visit 1.
7. To be switched to the inhaled mono-products (without changing the dose or substance) at least 12 hours prior to Visit 1.
8. Non-approved and according to international guidelines (e.g. GINA 2010 [P11-06175]) not recommended 'experimental' drugs for routine asthma therapy (e.g. TNF-alpha blockers, methotrexate, cyclosporine).

Source: Clinical trial protocol 205.443, Table 4.2.2.1:1, p50

Study Treatments

At Visit 2, subjects were randomized equally to one of three blinded treatment arms:

- 2.5 µg tiotropium inhalation solution daily (2 actuations of 1.25 µg)
- 5 µg tiotropium inhalation solution daily (2 actuations of 2.5 µg)
- Placebo inhalation solution daily (2 actuations)

All study treatments were orally inhaled via the Respimat inhaler in the afternoon (~3 p.m. to 5 p.m.) at approximately the same time each day (-30 minutes to +2 hours from time of administration at Visit 2). If the afternoon dose was forgotten, patients were allowed to take the dose later up until 10 p.m., after which the dose should have been skipped and taken the next day at the scheduled time. For patients 1 to 4 years of age, the Respimat was used in combination with the Aerochamber Plus Flow-Vu valved holding chamber with facemask. Children who were 5 years of age at Visit 1 were allowed to inhale from the Respimat without a spacer at the discretion of the investigator; however, the method of delivery was to remain stable throughout the trial (i.e., with or without a spacer).

For rescue medication, the Applicant provided patients with open label salbutamol/albuterol HFA MDIs (100 µg/puff) to be used as needed; nebulized salbutamol/albuterol was allowed but not provided by the Applicant.

Efficacy Assessments

The following section describes efficacy variables evaluated in the study. The timing of assessments is provided in Table 11 and Appendix, Table 33.

Pediatric Asthma Caregiver Diary (PACD)

The PACD consists of a total of ten questions to be completed by parents/caregivers: three questions for each morning upon waking and seven questions for each evening upon going to sleep (see Appendix, Figure 14). The diary was designed to evaluate daily asthma symptoms in children aged 2 to 5 years and has been evaluated in a single study.[6]

Pulmonary Function Testing

PFTs were only performed in patients who were 5 years of age and capable of reproducing PFTs of acceptable quality; patients were required to produce at least two acceptable curves where the second highest FVC and FEV_1 were within 0.1L or 10% of the highest value, whichever was greater. Spirometry was conducted with patients in the seated position having abstained from SABA and LABA medications for 8 and 12 hours, respectively. At each time point, FEV_1 and FVC were measured from a series of at least three spirometric maneuvers (repeatability criteria were used to determine when more than three FVC maneuvers were needed with an upper limit of 8 attempts). The highest FEV_1 and FVC from an acceptable maneuver were recorded regardless of whether or not they came from different spirometric maneuvers. PFTs were performed

[6] Santanello NC, DeMuro-Mercon C, Davies G, et. al. J Allergy Clin Immunol. 2000; 106(5): 861-866

at Visits 1, 2, and 5. PFTs from Visit 1 were used to confirm acceptable quality, and were not necessary if there was recent documentation that the patient was not able to perform technically acceptable PFTs. At Visits 2 and 5, baseline PFTs were performed 10 minutes pre-dose (window of 5 to 25 minutes prior to dose). After this measurement, patients took their usual maintenance therapy (except LABAs) followed by first dose of study medication. After the end of the second inhalation of study medication, PFTs were repeated at 30 and 60 minutes (± 5 minutes), 2 and 3 hours (± 10 minutes) post-dose as shown in Appendix, Table 33.

Caregiver's Global Impression of Change (CGI-C)
Caregivers evaluated the overall treatment effect at the end of the 12 week treatment period compared to prior to randomization. Using a 7-point scale, caregivers answered the following question:

> "Check the one number that best describes how your child's asthma is now, compared with how it was before your child began taking medications in this study."
>
> 1. very much better
> 2. much better
> 3. a little better
> 4. no change
> 5. a little worse
> 6. much worse
> 7. very much worse

Additional Diary Card
A paper diary card in addition to the PACD was provided to patients/caregivers for completion each morning (see Appendix, Figure 15).

Interrupter resistance technique (Rint) and Impulse oscillometry (IOS)
Rint and IOS measurements were optional methods to measure airway resistance in 2-5 year old patients capable of performing the tests and those not already participating in PFTs. Patients performed Rint only if not in the IOS subset, and vice versa. Testing was conducted according to ATS/ERS guidelines.[7] Measurements were obtained at Visit 2 (baseline) and Visit 5, 10 minutes pre-dose, and then 30 minutes post-dose.

Safety Variables and Endpoints
Safety assessments included collection of adverse events/adverse events of special interest (hepatic injury), vital signs, physical exam, 12-lead ECG, and clinical labs (hematology, chemistry) according to the schedule in

[7] Beydon N. et al. Am J Respir Crit Care Med. 2007; 175: 1304-1345

Table 11. Schedule of Assessments: Study 443

Trial phase	Screening /run-in		Treatment							FU
Visit[1]	0	1	2	☎	3	☎	4	☎	5	6
Week		-2	0	2	4	6	8	10	12	15
Day		-14	1	15	29	43	57	71	85	V5+21
Flexibility (+/- days)[2]		-7		±4	±2	±4	±2	±4	±2	+7
Informed consent/assent	X[3]									
Demographics		X								
Height and weight		X							X	
Medical history/baseline conditions		X								
Asthma background		X								
In-/Exclusion criteria	X[3]	X	X							
Physical examination		X							X[4]	X
Laboratory testing[5]		X							X[4]	
IVRS/IWRS[17]		X	X		X		X		X	
Randomisation			X							
Training in use of Respimat® (with or without spacer)		X	X							
Check medication wash-out compliance and compliance regarding restricted medication[6]		X	X		X		X		X	
Check study medication compliance					X		X		X[4]	
Administer study medication[7]			X		X		X		X	
Dispense study medication			X		X		X			
Dispense rescue medication	X	X	X		X		X		X	
Collect study medication					X		X		X[4]	
Spirometry (PFT)[8]		X[9]	X[10]						X[10]	
Interrupter resistance (Rint)[11]		X[12]	X[13]						X[13]	
Impulse oscillometry (IOS)[11]		X[12]	X[13]						X[13]	
Vital signs[14]		X	X		X		X		X[4]	X
12-lead ECG		X							X[4]	
Pharmacokinetic urine sampling[15]			X						X	
Dispense PACD and additional diary card		X	X		X		X			
Review/collect PACD and additional diary card			X		X		X		X[4]	
Assessment of asthma control[16]		X	X							
Caregiver's global impression of change (CGI-C)									X[18]	
Adverse events (AE)		X	X	X	X	X	X	X	X[4]	X
Concomitant therapy		X	X	X	X	X	X	X	X[4]	X
Drug accountability			X		X		X		X[4]	
Termination of study medication									X[4]	
Trial completion										X

1. Visit 2 to 5 should be scheduled in the afternoon at a time that allows dosing of study medication in the clinic. Visit 0, 1 and 6 may be conducted any time during regular business hours. Scheduled phone calls may be placed at any (convenient) time during the day. The follow up visit should be scheduled 21 days (+ 7 days) after the last dose of study medication (including for patients who discontinue early).
2. Each Respimat® inhaler contains drug supply for 30 days.
3. Patient's parents (or legal guardian) must sign (after ample time to decide) an informed consent consistent with the International Conference on Harmonisation (ICH) - Good Clinical Practice (GCP) guidelines prior to participation in the trial and any study-related procedure, including medication wash-out and restrictions. Where appropriate, participants should assent to enroll in the study (age of assent to be determined by Institutional Review Boards (IRB's) / Independent Ethics Committees (IEC's) or be consistent with local legal requirements) (see Section 8.1). A preliminary check of in-/exclusion criteria is strongly recommended at Visit 0, to avoid unnecessary wash-out procedures in non-eligible patients. The interval between Visit 0 (signing of informed consent) and Visit 1 (screening) may be between 0 and 28 days, depending on wash-out requirements and local regulations.
4. To be completed by all patients who took at least 1 dose of study medication including those who discontinue early.
5. Haematology and blood chemistry. Topical (percutaneous) analgesia to reduce pain associated with venipuncture, e.g. amethocaine gel or EMLA cream (Eutectic Mixture of Local Anaesthetics), must be applied (may only be omitted in patients who explicitly refuse it). Visit 1 laboratory parameters blood eosinophil count, white blood cell count, creatinine levels and total serum IgE levels will be documented in the electronic Case Report Form (eCRF). The IgE result does not need to be available prior to randomization. **If total serum IgE levels have been obtained within 6 months prior to Visit 1 (and are available in the patients medical file), the measurement does not need to be repeated at Visit 1 (the historic value may be used).**
6. Refer to Section 4.2.2.1.
7. Study medication should be administered as described in Section 4.1.4.
8. Pulmonary Function Testing (PFT) will only be performed in 5 year olds who are capable of providing PFTs of acceptable quality.
9. To confirm acceptable quality. It is not necessary to perform this PFT if the medical files provide clear evidence that the patient (at the age of 5 years) is not able to perform technically acceptable PFTs
10. PFTs are performed -10 minutes prior to trial drug administration and 30 minutes, 1 h, 2 h and 3 h post dose.
11. Rint or IOS measurements are optional and will only be performed in 2-5 year old patients able to perform technically acceptable Rint or IOS measurements and who are not participating in the PFT subset.
12. To confirm acceptable quality. It is not necessary to perform this measurement if the medical files provide clear evidence that the patient (at the current age) is not able to perform technically acceptable measurements.
13. Measurements are performed -10 minutes prior to trial drug administration and 30 minutes post dose.
14. At Visit 1, prior to blood sampling and (if applicable) prior to spirometry/Rint/IOS. At Visits 2, 3, 4 and 5 prior to dosing (and if applicable prior to the pre-dose PFT/Rint/IOS).
15. Urine will be collected from approximately 24 patients before study drug administration (-1 h to 0 h) and in the 0-2 and 2-3 hours post-dose intervals following inhalation of the study medication via the Respimat® inhaler. Time point zero for pharmacokinetic sampling is defined as the end of inhalation from the Respimat® inhaler.
16. Levels of asthma control as described in the GINA guideline [P11-00966].
17. Visit 1 must be registered in IVRS/IWRS (during the visit). At Visit 2 to Visit 4 study medication will be issued using IVRS/IWRS (to eligible patients). At Visit 5 the end of the treatment period must be registered in IVRS/IWRS (during the visit). When applicable, screen failure or early discontinuation needs to be registered in IVRS/IWRS.
18. The CGI-C should be completed prior to other visit assessments and should precede any discussions with a health professional (physician, nurse or study co-ordinator).

Source: Clinical Trial Protocol 205.443, Flow Chart, p5

Efficacy Endpoints

The primary endpoint for all patients was the change from baseline in the mean combined daytime asthma symptom score as measured by the Pediatric Asthma Caregiver Diary (PACD) in the last week of the 12 week treatment period. Baseline was defined as the mean value of daily daytime scores during the last 7 days prior to Visit 2. The mean daily daytime score was the average of scores of questions 4 to 7.

The co-primary endpoint for children 5 years of age who were able to perform technically acceptable and reproducible PFTs was the FEV_1 $peak_{0\text{-}3h}$ response (i.e., difference from baseline) at week 12.

Secondary endpoints included:

- Change from baseline in the mean daily overnight asthma symptom score measured by the PACD in the last week of the 12 week treatment period
- Percentage of days without asthma symptoms during the 12 week treatment period. A day without symptoms was defined as a day during which the patient experienced no daytime or nighttime asthma symptoms (PACD questions 1, and 4-7), did not use rescue medication (PACD questions 2 and 9), and had no asthma exacerbation/worsening requiring systemic corticosteroids, unscheduled visits to the doctor, ED, or hospital (PACD question 8).
- Percentage of days with use of PRN rescue medication during the 12-week treatment period
- Nighttime awakenings due to asthma symptoms as assessed by the additional diary card

Additional secondary endpoints for children 5 years of age who performed PFTs:

- Trough FEV_1 response at Week 12
- FVC $peak_{0\text{-}3h}$ and trough response at Week 12
- FEV_1 ($AUC_{0\text{-}3h}$) and FVC ($AUC0_{\text{-}3h}$) response at Week 12
- Individual FEV_1 and FVC response measurements at Week 12

Other Endpoints

- Change from baseline in mean daily combined daytime asthma symptom score per week during the 12 week treatment period
- Change from baseline in the mean individual daytime score and the mean individual overnight score per week during the 12 week treatment period
- Percentage of patients requiring systemic corticosteroid rescue for asthma during the 12-week treatment period
- Frequency of asthma attacks, defined as worsening of asthma requiring systemic corticosteroid rescue or an unscheduled visit to the doctor, ED, or hospital
- Nighttime awakenings due to asthma symptoms as assessed by the additional diary card
- Caregiver's global impression of change (CGI-C) at week 12

Other endpoints for children aged 5 years who performed PFTs

- Individual FEV_1 and FVC response measurements at Visit 2 ($peak_{0-3h}$, trough, AUC_{0-3h})

Other endpoints for patients participating in Rint measurements (and not in the PFT or IOS subset)

- Change from baseline in absolute value of $Rint_{exp}$ at Day 1 and Week 12 of treatment
- Change from baseline in Z-score at Day 1 and Week 12 of treatment for children ≥ 90 cm and ≤ 160 cm tall

Other endpoints for patients participating in IOS measurements (and not in PFT or Rint subset)

- Change from baseline in absolute value of Rrs5 at Day 1 and Week 12
- Percentage of change in Rrx5 from baseline at Day 1 and Week 12
- Change from baseline in absolute value of Xrs5 at Day 1 and Week 12
- Percentage of change in Xrs5 from baseline at Day 1 and Week 12

Statistical Analyses

No formal hypothesis testing was performed. All treatment comparisons were exploratory, and therefore, there was no control for multiplicity. Summary of safety data and efficacy analyses were based on all randomized patients who received at least one dose of trial medication (Treated Set or Full Analysis Set). An analysis of covariance (ANCOVA) with treatment as fixed effect and baseline as covariate were performed for the primary endpoint of change from baseline in mean daily daytime asthma score from the PACD in the last week of the 12 week treatment period. The co-primary endpoint of FEV_1 $peak_{(0-3h)}$ response at week 12 for children 5 years of age was analyzed descriptively and presented by treatment group. ANCOVA was performed for secondary and other efficacy endpoints if applicable (except endpoints based on PFT and Rint and IOS measurements). Descriptive statistics by treatment group were presented for all secondary, other efficacy, and safety endpoints.

6 Review of Efficacy

Efficacy Summary

The primary clinical data to support the efficacy of tiotropium Respimat (TioR) for the indication of long-term, once-daily, maintenance treatment of asthma in 6 to 11 year old patients consisted of one 48-week trial in patients with moderate asthma (Study 445) and one 12-week trial in patients with severe asthma (Study 446). Both trials were randomized, double-blind, placebo-controlled, and parallel group in design and evaluated two doses of TioR, 2.5 µg and 5 µg administered once daily. The primary and key secondary endpoints in both trials were peak FEV_1 measured within 3 hours post-dose (FEV_1 $peak_{(0-3)}$) and trough FEV_1, respectively. In addition to lung function parameters, other efficacy outcomes included measures of asthma control (ACQ-IA),

asthma quality of life (PAQLQ), rescue medication use, asthma exacerbations, and asthma symptom control.

In the studies of 6 to 11 year old patients, the approved dose of TioR for asthma, 2.5 µg once daily, demonstrated statistically significant improvements in FEV_1 $peak_{(0-3)}$ and trough response in patients with moderate persistent asthma (445), but showed no significant difference from placebo in patients with severe persistent asthma (446). The difference from placebo for FEV_1 $peak_{(0-3)}$ was 0.170 L and 0.035 L in studies 445 and 446 at weeks 24 and 12, respectively. The difference from placebo for trough FEV_1 was 0.116 L and 0.018 L, again at weeks 24 and 12 respectively. By comparison, the higher dose of TioR, 5 µg once daily, demonstrated statistically significant responses in FEV_1 $peak_{(0-3)}$ and trough compared to placebo in both studies. The difference from placebo for FEV_1 $peak_{(0-3)}$ was 0.164 L and 0.139 L, at 24 and 12 weeks respectively, and 0.118 L and 0.087 L for trough FEV_1, at the same respective time points. Despite superiority for the primary and key secondary lung function endpoints, neither trial showed significant effects on patient or caretaker-reported outcomes such as the ACQ-IA, PAQLQ, or asthma symptom score or in rescue medication use. Regarding asthma exacerbations, there were a similar number of events across treatment groups in study 445 over 48 weeks, and fewer events in the TioR 2.5 group compared to placebo and TioR5 in study 446 over 12 weeks.

In study 445, similar FEV_1 peak and trough responses were observed with both doses at the primary analysis time point (week 24) as well as at other time points throughout the study (weeks 12 and 48) with no added bronchodilator benefit for the higher dose. However, in study 446, only the higher 5 µg dose demonstrated statistically significant improvements in FEV_1. The discrepancy in results might be explained by the difference in study population asthma severity. Patients in study 446 had severe persistent asthma with a majority receiving concomitant LABA therapy during the study while patients in study 445 had moderate persistent asthma and were required to discontinue LABA therapy prior to enrollment. It is possible that a higher dose of tiotropium Respimat is required to produce an additional bronchodilator effect in patients on background LABA therapy, albeit, this was not the case in the trial of adolescent patients with severe asthma (Study 205.456) described in previous reviews. Regardless, drawing from experience in the phase 3 adult and adolescent asthma trials, the spirometric data consistently indicated that TioR 2.5 had an equivalent, if not improved, bronchodilator treatment effect compared to TioR 5 with similar effects on reduction of asthma exacerbations. Given that efficacy of TioR in the proposed 6 to 11 year old age group is based partially on extrapolation of efficacy in adults and adolescents, TioR 2.5 once daily still appears to be the most appropriate dose for this age group for the treatment of persistent asthma on top of ICS therapy.

(b) (4)

(b) (4)

In sum, there is substantial evidence of efficacy in 6 to 11 year old patients with persistent asthma to recommend approval of TioR 2.5 µg once daily for the long-term, once daily maintenance treatment of asthma. (b) (4)

6.1 Indication

In this sNDA, the proposed indication for tiotropium Respimat is for the long-term, once-daily, maintenance treatment of asthma in patients (b) (4) of age and older.

6.1.1 Methods

The efficacy review in pediatric patients (b) (4) is based on three trials: Studies 445 and 446 in 6 to 11 year old patients with moderate and severe asthma, respectively, and Study 443 in 1 to 5 year old patients with persistent asthma. Given that inhaler products are not typically indicated for children under 5 years of age due to the need for combined use with a spacer device and because efficacy endpoints in Study 443 were exploratory in nature, my review focuses on the efficacy evaluation in 6 to 11 year old patients and discusses results in 1 to 5 year olds separately under Section 6.1.10.

6.1.2 Demographics

The following tables show the demographics and baseline disease characteristics of patients in the treated set (TS) of each study. In all studies, patients tended to be atopic, white, male, and toward the older end of the studied age range. While some minority racial/ethnic groups were underrepresented relative to the proportion of the population affected by the disease, other minority racial/ethnic groups were overrepresented. Overall, there were no meaningful differences between treatment groups in any study.

Table 12. Demographic and Baseline Characteristics: Study 445

Demographic Parameters	Placebo N=131	TioR 2.5 N=135	TioR 5 N=135
Age (years)			
Mean (SD)	8.9 (1.7)	8.9 (1.6)	8.9 (1.7)
Median	9	9	9
Age groups, n (%)			
6 – 8 years	49 (37)	53 (39)	59 (44)
9 – 11 years	82 (63)	82 (61)	76 (56)
Gender, n (%)			
Female	46 (35)	38 (28)	53 (39)
Race, n (%)			
White	112 (85)	113 (84)	114 (84)
American Indian / Alaska Native	16 (12)	15 (11)	14 (10)
Black/African American	1 (1)	3 (2)	3 (2)
Asian	2 (2)	4 (3)	4 (3)
Ethnicity, n (%)			
Hispanic/Latino	18 (14)	18 (13)	19 (14)
Baseline lung function, pre-bronchodilator (mean)[1]			
FEV_1 (L)	1.673	1.622	1.595
FEV_1 (% predicted normal)	86	84	83
FVC (L)	2.187	2.092	2.085
FEV_1/FVC (%)	78	78	78
Baseline lung function, post-bronchodilator (mean)[2]			
FEV_1 (L)	1.920	1.897	1.881
FEV_1 (% predicted normal)	99	98	98
Reversibility (mL)	378	407	375
Medical History, n (%)			
Prematurity	0	5 (4)	3 (2)
Second hand smoke exposure	11 (8)	11 (8)	7 (5)
Atopic dermatitis/eczema	19	23	21
Food allergy	1 (1)	7 (5)	2 (2)
Allergic rhinitis/seasonal allergy	84 (64)	82 (61)	83 (62)
Asthma History (years)			
Age at Onset (mean)	4.7	4.5	4.8
Duration			
Mean	4.2	4.4	4.1
< 1 year	10 (8)	7 (5)	5 (4)

Demographic Parameters	Placebo N=131	TioR 2.5 N=135	TioR 5 N=135
1 to < 3 years	29 (22)	33 (24)	46 (34)
≥ 3 years	92 (70)	95 (70)	84 (62)
Concomitant Medications[3]			
Oral corticosteroids	1	2 (2)	0
LABA	20 (15)	31 (23)	21 (16)
Anticholinergics (short-acting)	3 (2)	3 (2)	3 (2)
Leukotriene modifiers	36 (28)	46 (34)	40 (30)
Xanthines	1 (1)	0	0
Omalizumab	0	0	0

[1]Measured 10 minutes prior to inhalation of study medication at Visit 2
[2]Measured 15-30 minutes after inhalation of 4 puffs salbutamol 100 µg at Visit 1
[3]Within 3 months of Visit 1
Source: CSR Tables 11.2.1:1, 11.2.5:1, 11.2.5:2, 15.1.4.1:1, 15.1.4.2:1, and 15.1.4.4:1 and MH dataset

Table 13. Demographic and Baseline Characteristics: Study 446

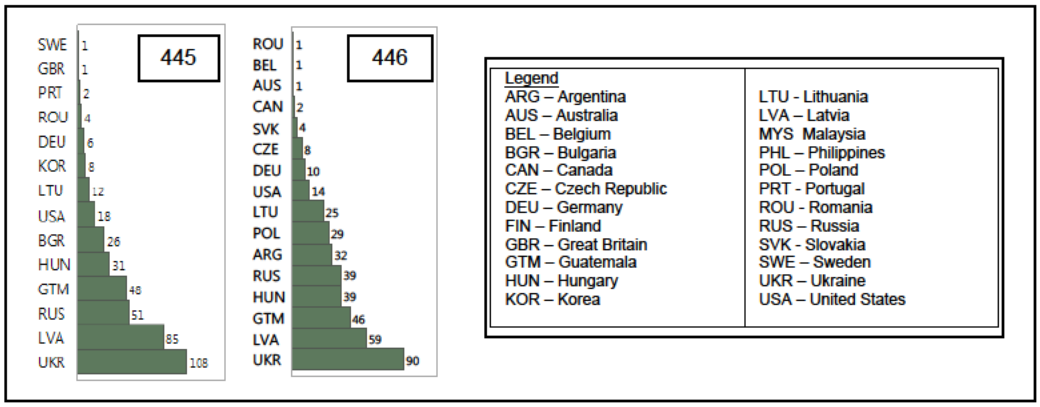
Demographic Parameters	Placebo N=134	TioR 2.5 N=136	TioR 5 N=130
Age (years)			
Mean (SD)	9.1 (1.6)	8.8 (1.7)	9.2 (1.6)
Median	9	9	9
Age groups, n (%)			
6 – 8 years	49 (37)	60 (44)	36 (28)
9 – 11 years	85 (63)	76 (56)	94 (72)
Gender, n (%)			
Female	41 (31)	40 (29)	40 (31)
Race, n (%)			
White	121 (90)	122 (90)	115 (89)
American Indian / Alaska Native	11 (8)	11 (8)	13 (10)
Black/African American	1 (1)	3 (2)	1 (1)
Asian	1 (1)	0	1 (1)
Ethnicity, n (%)			
Hispanic/Latino	28 (21)	23 (17)	21 (16)
Baseline lung function, pre-bronchodilator (mean)[1]			
FEV_1 (L)	1.552	1.569	1.595
FEV_1 (% predicted normal)	80	84	81
FVC (L)	2.013	2.057	2.093
FEV_1/FVC (%)	78	77	77
Baseline lung function, post-bronchodilator (mean)[2]			
FEV_1 (L)	1.862	1.828	1.924
FEV_1 (% predicted normal)	97	98	97
Reversibility (mL)	392	387	412
Medical History, n (%)			
Prematurity	7 (5)	4 (3)	6 (5)
Second hand smoke exposure	9 (7)	10 (7)	12 (9)
Atopic dermatitis/eczema	18 (13)	10 (7)	14 (11)
Food allergy	3 (2)	1 (1)	3 (2)
Allergic rhinitis/seasonal allergy	81 (60)	87 (64)	89 (69)

Demographic Parameters	Placebo N=134	TioR 2.5 N=136	TioR 5 N=130
Asthma History (years)			
Age at Onset (mean)	4.4	3.9	4.1
Duration			
Mean	4.8	5.0	5.1
< 1 year	5 (4)	2 (2)	7 (5)
1 to < 3 years	25 (19)	36 (27)	23 (18)
≥ 3 years	104 (78)	98 (72)	100 (77)
Concomitant Medications[3]			
Systemic corticosteroids	2 (2)	3 (2)	2 (2)
LABA	101 (75)	113 (83)	101 (78)
Anticholinergics (short-acting)	1 (1)	4 (3)	3 (2)
Leukotriene modifiers	113 (84)	113 (83)	114 (88)
Xanthines	9 (7)	9 (7)	11 (9)
Omalizumab	0	0	0

[1]Measured 10 minutes prior to inhalation of study medication at Visit 2
[2]Measured 15-30 minutes after inhalation of 4 puffs salbutamol 100 µg at Visit 1
[3]Within 3 months of Visit 1
Source: CSR Tables 11.2.1:1, 11.2.5:1, 11.2.5:2, 15.1.4.1:1, 15.1.4.2:1, and 15.1.4.4:1 and MH dataset

Patients from the U.S. comprised 4% of each study population in Studies 445 and 446.

Figure 4. Geographic Distribution of Subjects in Studies 445 and 446



6.1.3 Subject Disposition

The tables below detail the disposition of subjects in each study. Overall, there were high rates of study completion across treatment groups.

Table 14. Subject Disposition: Study 445

	Placebo	TioR 2.5	TioR 5
Randomized	132	136	135
Treated, n (%)	131 (100)	135 (100)	135 (100)
Completed trial medication	122 (93)	130 (96)	130 (96)
Prematurely discontinued	9 (7)	5 (4)	5 (4)
Adverse events	0	0	0

	Placebo	TioR 2.5	TioR 5
Lack of efficacy	0	0	0
Non-compliant with protocol	1 (1)	0	0
Lost to follow-up	0	2 (2)	0
Consent withdrawn (not due to AE)	4 (3)	3 (2)	2 (2)
Other	4 (3)	0	3 (2)
Source: CSR 205.445, Table 10.1:1			

Table 15. Subject Disposition: Study 446

	Placebo	TioR 2.5	TioR 5
Randomized	134	137	130
Treated, n (%)	134 (100)	136 (100)	130 (100)
Completed trial medication	130 (97)	136 (100)	126 (97)
Prematurely discontinued	4 (3)	0	4 (3)
Adverse events	2 (2)	0	4 (3)
Worsening of asthma	0	0	2 (2)
Lack of efficacy	0	0	0
Non-compliant with protocol	0	0	0
Lost to follow-up	0	0	0
Consent withdrawn (not due to AE)	1 (1)	0	1 (1)
Other	1 (1)	0	1 (1)
Source: CSR 205.446, Table 10.1:1			

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint in 6 to 11 year old patients was FEV_1 $peak_{0\text{-}3h}$ response at 24 and 12 weeks of treatment in trials 445 and 446, respectively. FEV_1 $peak_{0\text{-}3h}$ was defined as the highest FEV_1 measured within the first 3 hours post-dosing. FEV_1 $peak_{0\text{-}3h}$ response was defined as the change of FEV_1 $peak_{0\text{-}3h}$ from baseline at Visit 2.

Primary and secondary analyses were conducted using the Full Analysis Set (FAS) population, all patients who took at least one dose of study medication.

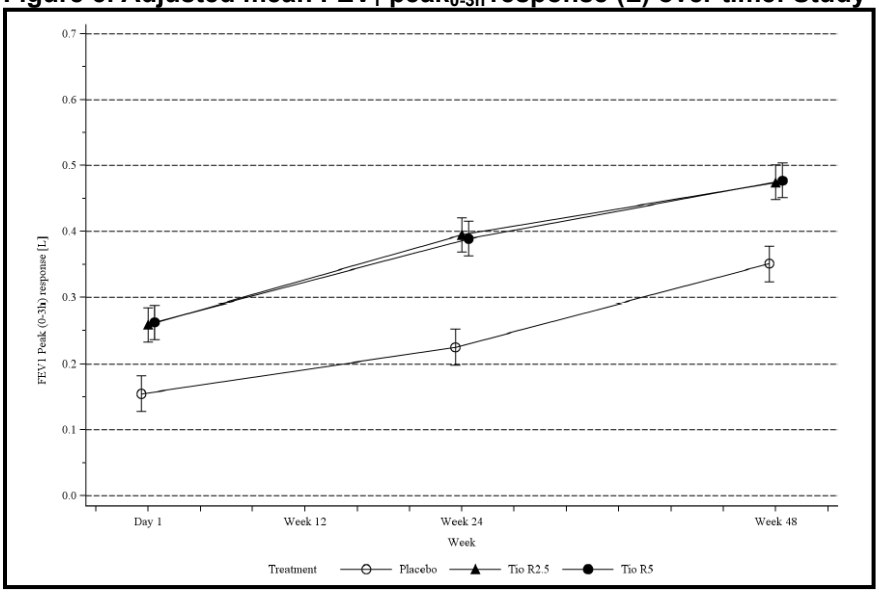
In Study 445, both doses of TioR demonstrated similar statistically significant increases in FEV_1 $peak_{0\text{-}3h}$ over placebo at week 24 that persisted through the end of the study at week 48 (Figure 5). In contrast, only the higher dose of TioR demonstrated a significant difference from placebo at week 12 (end of treatment) in study 446. While it is possible that patients with severe persistent asthma on concomitant LABA therapy may have required a higher dose of TioR to experience additional improvements in lung function or those on LABA therapy may inherently have more difficult to treat asthma, the study was not designed to specifically address this question. Refer to the biostatistics review by Dr. Robert Abugov for exploratory analyses related to concomitant LABA use in study 446.

Table 16. Peak$_{(0\text{-}3h)}$ FEV$_1$ in 6 to 11 year old Subjects (FAS population)

Trial	Background Medication	Treatment	N	Adjusted mean baseline FEV$_1$ Peak$_{(0\text{-}3h)}$ in mL (SE)	Adjusted mean FEV$_1$ Peak$_{(0\text{-}3h)}$ response in mL (SE)	Difference vs placebo (95% CI)
Week 24						
445	Medium-dose ICS ± other controllers (except LABAs)	Placebo	126	155 (27)	225 (27)	--
		TioR 2.5	131	259 (26)	395 (26)	170 (108, 231)
		TioR 5	134	263 (26)	389 (26)	164 (103, 225)
Week 12						
446	High-dose ICS + 1 controller OR medium-dose ICS + 2 controllers	Placebo	130	183 (25)	252 (25)	--
		TioR 2.5	135	242 (25)	287 (25)	35 (-28, 99)
		TioR 5	128	293 (26)	391 (26)	139 (75, 203)

Abbreviations: FAS=Full Analysis Set, SE=standard error, ICS=inhaled corticosteroid, LABA=long-acting beta-agonist, CI=confidence interval, TioR=tiotropium Respimat
Source: CSR 205.445 and 205.446, Tables 11.4.1.1.1:1 and 15.2.1.1:1
Adjusted for treatment, country, visit, study baseline, treatment*visit and study baseline*visit

Figure 5. Adjusted mean FEV$_1$ peak$_{0\text{-}3h}$ response (L) over time: Study 445 (FAS population)



Source: CSR 205.445, Figure 11.4.1.1.1:1

6.1.5 Analysis of Secondary Endpoints(s)

The key secondary endpoint in studies 445 and 446 was trough FEV$_1$, an important clinically relevant outcome measure for a maintenance therapy not intended for use as an acute bronchodilator because it demonstrates lung function improvement over the entire dosing interval. In the TioR adult asthma program, trough and peak$_{0\text{-}3h}$ FEV$_1$ were co-primary endpoints.

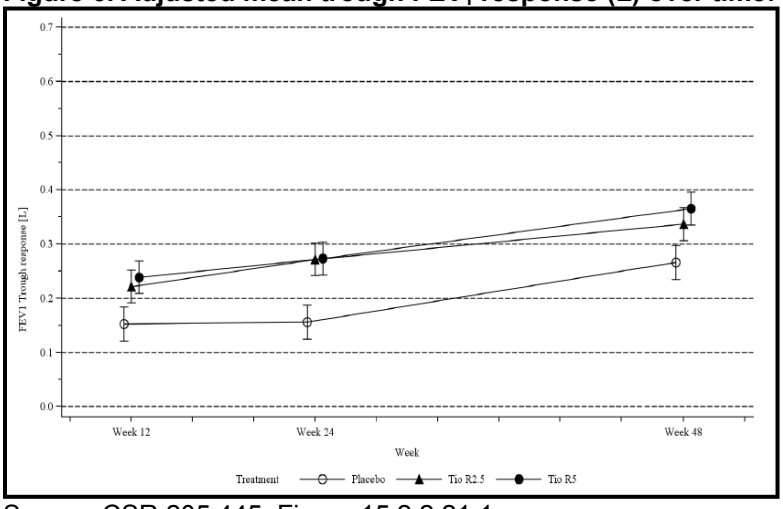
Similar to results for the primary endpoint, results for trough FEV_1 response were similar between TioR2.5 and TioR5 groups at week 24 (Table 17) as well as week 48 (Figure 6) in Study 445, whereas only the high dose demonstrated a difference from placebo in Study 446.

Table 17. Key secondary endpoint: Trough FEV_1 response in 6 to 11 year old subjects (FAS population)

Trial	Background Medication	Treatment	N	Adjusted mean trough FEV_1 response in mL (SE)	Difference vs placebo (95% CI)
Week 24					
445	Medium-dose ICS ± other controllers (except LABAs)	Placebo	126	156 (31)	--
		TioR 2.5	131	272 (30)	116 (46, 186)
		TioR 5	134	274 (30)	118 (48, 188)
Week 12					
446	High-dose ICS + 1 controller OR medium-dose ICS + 2 controllers	Placebo	130	136 (27)	--
		TioR 2.5	135	154 (26)	18 (-48, 85)
		TioR 5	128	223 (27)	87 (19, 154)

Abbreviations: FAS=Full Analysis Set, SE=standard error, CI=confidence interval, TioR=tiotropium Respimat
Source: CSR 205.445 and 205.446, Tables 15.2.2.1:1
Adjusted for treatment, country, visit, baseline, treatment*visit, baseline*visit
Baseline mean FEV1 (L) at Visit 2 = 1.629 (Study 445) and 1.572 (Study 446)

Figure 6. Adjusted mean trough FEV_1 response (L) over time: Study 445 (FAS population)



Source: CSR 205.445, Figure 15.2.2.21:1

Additional lung function-related secondary endpoints in 6 to 11 year old patients are shown in Table 18. Results were consistent with the primary and key secondary endpoints in that similar positive treatment effects were observed in the TioR 2.5 and TioR 5 groups over placebo at weeks 24 and 48 in Study 445 while only the TioR 5 group demonstrated statistically significant differences from placebo in Study 446.

Table 18. Lung function secondary endpoints in 6 to 11 year old subjects (FAS population)

Endpoints	Placebo	TioR 2.5	TioR 5
Trial 445			
Week 24	**N=126**	**N=131**	**N=134**
FEV_1 AUC_{0-3h}			
Adjusted mean response in mL (SE)	152 (26)	306 (25)	309 (25)
Adjusted mean difference vs placebo (95% CI)	--	154 (95, 212)	157 (98, 215)
FVC $peak_{0-3h}$			
Adjusted mean response in mL (SE)	215 (33)	325 (32)	307 (32)
Adjusted mean difference vs placebo (95% CI)	--	110 (36, 184)	91 (18, 165)
FVC AUC_{0-3h}			
Adjusted mean response in mL (SE)	130 (30)	235 (29)	207 (29)
Adjusted mean difference vs placebo (95% CI)	--	105 (37, 172)	76 (9, 143)
Trough FVC			
Adjusted mean response in mL (SE)	154 (35)	246 (34)	206 (34)
Adjusted mean difference vs placebo (95% CI)	--	92 (13, 171)	52 (-27, 131)
Week 48	**N=124**	**N=130**	**N=130**
FEV_1 $peak_{0-3h}$			
Adjusted mean response in mL (SE)	351 (27)	474 (26)	477 (26)
Adjusted mean difference vs placebo (95% CI)	--	124 (62, 185)	127 (65, 188)
Trough FEV_1			
Adjusted mean response in mL (SE)	266 (32)	337 (30)	365 (31)
Adjusted mean difference vs placebo (95% CI)	--	71 (1, 142)	99 (29, 170)
FVC $peak_{0-3h}$			
Adjusted mean response in mL (SE)	361 (33)	430 (32)	413 (32)
Adjusted mean difference vs placebo (95% CI)	--	69 (-5, 143)	52 (-22, 126)
Trough FVC			
Adjusted mean response in mL (SE)	280 (35)	341 (34)	333 (34)
Adjusted mean difference vs placebo (95% CI)	--	62 (-17, 141)	53 (-26, 133)
Trial 446			
Week 12	**N=130**	**N=135**	**N=128**
FEV_1 AUC_{0-3h}			
Adjusted mean response in mL (SE)	175 (23)	206 (22)	301 (23)
Adjusted mean difference vs placebo (95% CI)	--	31 (-26, 88)	126 (68, 184)
FVC $peak_{0-3h}$			
Adjusted mean response in mL (SE)	244 (28)	201 (27)	275 (28)
Adjusted mean difference vs placebo (95% CI)	--	-43 (-113, 27)	30 (-40, 101)
Trough FVC			
Adjusted mean response in mL (SE)	141 (29)	94 (29)	150 (30)
Adjusted mean difference vs placebo (95% CI)	--	-48 (-121, 26)	9 (-66, 83)
FVC AUC_{0-3h}			
Adjusted mean response in mL (SE)	145 (25)	105 (24)	182 (25)
Adjusted mean difference vs placebo (95% CI)	--	-41 (-103, 22)	37 (-26, 100)

Adjusted for treatment, country, visit, study baseline, treatment*visit, and study baseline*visit
Mean study baseline FEV1 (L) at Visit 2=1.629 (SD 0.393) for Study 445 and 1.572 (SD 0.346) for Study 446
Mean study baseline FVC (L) at Visit 2=2.121 (SD 0.564) for Study 445 and 2.054 (SD 0.475) for Study 446
Source: CSR 205.445 and 205.446, Tables 11.4.1.2.1:1

6.1.6 Other Endpoints

Efficacy results for other endpoints in 6 to 11 year old patients are described below.

Rescue medication use
Overall, use of rescue medication decreased in both studies with TioR as would be expected with the addition of a long acting bronchodilator treatment; however, there was no consistent significant difference from placebo with either dose of TioR.

Peak expiratory flow (PEF)
In both studies, at home measurements of PEF using the AM3 device fluctuated widely from week to week, but generally increased in the active treatment groups compared to placebo throughout the entire treatment period.

Asthma symptoms
There were no significant differences from placebo with regard to asthma symptom scores or symptom free days with either TioR dose in either study.

Asthma exacerbations
The number of patients who experienced a "severe" asthma exacerbation (defined as exacerbations requiring treatment with systemic corticosteroids) as well as the hazard ratio for time to first severe exacerbation in each study is shown in the table below. Overall, both the number of asthma exacerbations requiring systemic steroid therapy (severe) or hospitalization (serious) was relatively low and similar among treatment groups. While TioR 2.5 treatment was associated with fewer exacerbations in Study 446, this finding is in contrast to the lung function results in this study, and therefore may be due to chance.

Table 19. Asthma Exacerbations in Studies 445 and 446

	Placebo	TioR 2.5	TioR 5
Study 445, N	**131**	**135**	**135**
Number of subjects with severe exacerbation (%)	6 (5)	7 (5)	7 (5)
Hazard ratio vs placebo (95% CI)	--	1.14 (0.4, 3.4)	1.14 (0.4, 3.4)
Number of subjects with hospitalization due to asthma (%)	2 (2)	2 (2)	0
Study 446, N	**134**	**136**	**130**
Number of subjects with severe exacerbation (%)	8 (6)	3 (2)	7 (5)
Hazard ratio vs placebo (95% CI)	--	0.4 (0.1, 1.6)	1.0 (0.4, 2.9)
Number of subjects with hospitalization due to asthma (%)	1 (1)	1 (1)	3 (2)

Source: CSR 205.445 and 205.446, Tables 15.2.4.3:1 and 12.3.2:1

Interviewer Administered Asthma Control Questionnaire (ACQ-IA) and Pediatric Asthma Quality of Life Questionnaire (PAQLQ)
For each questionnaire, a change in ≥ 0.5 units has been identified as the minimally important difference and was used as the cutoff to define a "responder". While a change in ≥ 0.5 units in the overall mean score when different from placebo suggests a beneficial treatment effect, this analysis fails to capture individual treatment responses and appears falsely optimistic if scores in the placebo group worsen. Therefore, an evaluation of the ACQ-IA and PAQLQ responder rates were of greater interest and clinical relevance and are shown in the table below. Responder rate analyses for the

ACQ-IA and ACQ-IA-6 are shown in the table below. The ACQ-IA-6 eliminates question #7 pertaining to FEV_1, but retains the question related to rescue medication use. Similar responder rates were observed among all treatment groups at each time point evaluated.

Table 20. ACQ-IA and PAQLQ Responder Rates (% of subjects): Studies 445 and 446

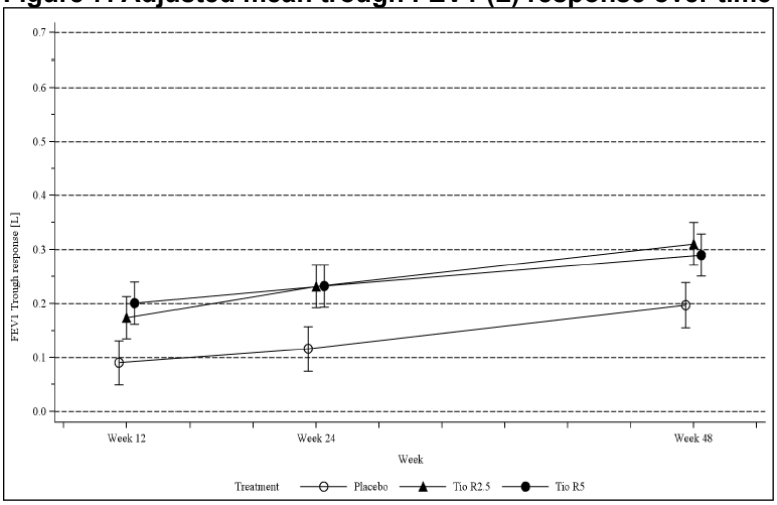
Study 445	Placebo	TioR 2.5	TioR 5
Week 24			
ACQ-IA	74	80	87
ACQ-IA-6	82	84	86
PAQLQ	51	61	54
Week 48			
ACQ-IA	87	87	87
ACQ-IA-6	88	90	88
PAQLQ	68	71	68
Study 446			
Week 12			
ACQ-IA	77	79	81
ACQ-IA-6	82	82	81

Source: CSR 205.445, Tables 15.2.3.3.1.1:2, 15.2.4.2.1:2, 15.2.3.3.2.1:2 and CSR 205.446, Tables 15.2.3.3.1.1:2 and 15.2.4.2.1:2

6.1.7 Subpopulations

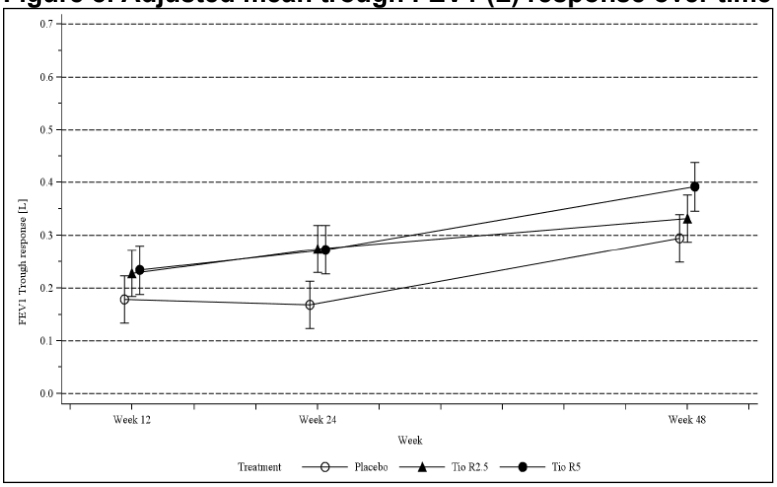
A subgroup analysis by age class (6-8 years vs 9-11 years) was also performed for the primary and key secondary endpoints. The results were generally consistent with the results in the overall population with no substantial differences between age groups.

Figure 7. Adjusted mean trough FEV1 (L) response over time in 6 to 8 year olds: Study 445



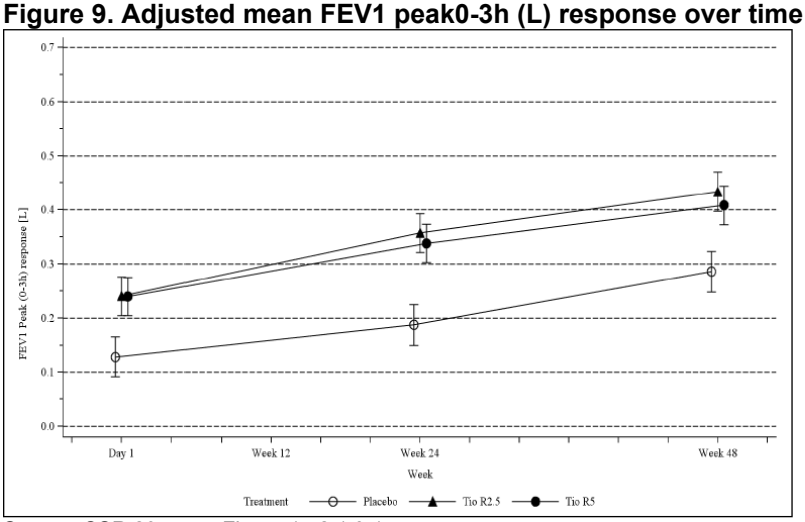
Source: CSF 205.445, Figure 15.2.2.1:2

Figure 8. Adjusted mean trough FEV1 (L) response over time in 9 to 11 year olds: Study 445



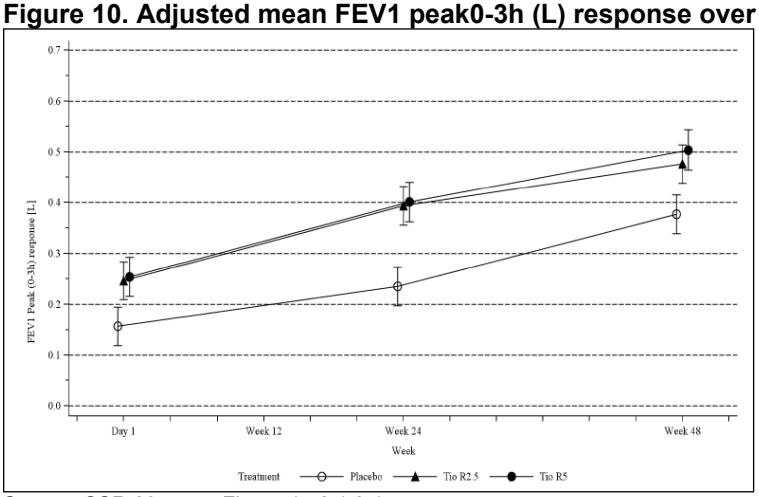
Source: 205.445, Figure 15.2.2.1:2

Figure 9. Adjusted mean FEV1 peak0-3h (L) response over time in 6 to 8 year olds: Study 445



Source: CSR 205.445, Figure 15.2.1.3:1

Figure 10. Adjusted mean FEV1 peak0-3h (L) response over time in 9 to 11 year olds: Study 445



Source: CSR 205.445, Figure 15.2.1.3:1

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

In 6 to 11 year old patients, similar efficacy results were observed for TioR 2.5 and TioR5 in the 48-week trial (445) in moderate asthma patients while only TioR 5 demonstrated statistically significant improvements in lung function over placebo in the 12-week trial (446) of patients with severe asthma. The discrepant results for the lower dose of TioR may potentially be explained by asthma severity and concomitant LABA medications. However, this was not the case in the 12-week trial of adolescents with severe asthma (Study 205.456), in which only the lower dose was statistically superior to placebo for both $peak_{0-3}$ and trough FEV_1. It is worth noting that clinical trials in patients <12 years of age with asthma were designed and initiated prior to approval of TioR 2.5 in adults and adolescents. While both TioR 5, the approved dose for COPD, and a lower dose of TioR 2.5 were evaluated in most of the adult and adolescent trials, the lower dose was ultimately approved because it consistently numerically outperformed the higher dose as a bronchodilator while demonstrating similar reductions in asthma exacerbations. Given the totality of data favoring TioR 2.5 over TioR 5 across the entire asthma development program, it is reasonable to select the same 2.5 µg daily dose for approval in the 6 to 11 year old age group.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

In Study 445, time profile curves for both trough and $peak_{0-3h}$ FEV_1 demonstrated a persistent bronchodilator effect for the 48-week duration of the trial. Similar findings were observed in the 24-48 week trials in adults and adolescents with asthma.

6.1.10 Additional Efficacy Issues/Analyses

This section will cover the review of efficacy data in 1 to 5 year old patients from Study 443.

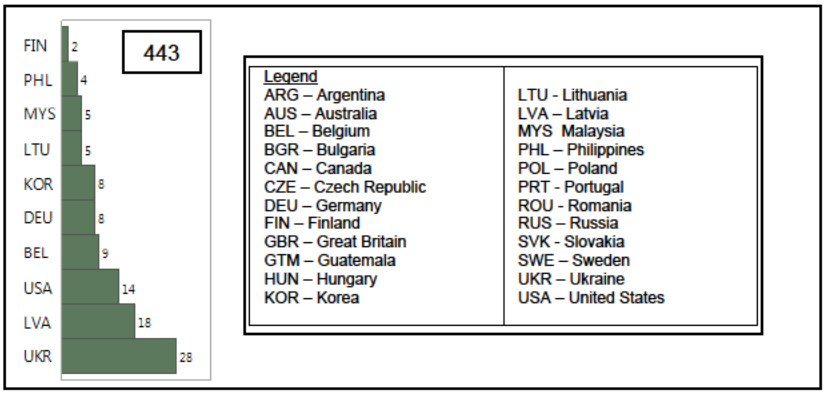
The following table shows the demographics and baseline disease characteristics of patients in the treated set (TS) of Study 443. Similar to studies in 6 to 11 year olds, these patients tended to be atopic, white, male, and toward the older end of the studied age range. Notably, a relatively sizable proportion of patients had been on LABA therapy within 3 months prior to randomization, which potentially provides additional reassurance that these patients were more likely to have persistent symptoms rather than intermittent wheeze that is typical of this younger age group or perhaps may be reflective of more widespread use of LABAs in pediatric patients outside of the US. Overall, there were no meaningful differences between treatment groups in any study.

Table 21. Demographic and Baseline Characteristics: Study 443

Demographic Parameters	Placebo N=34	TioR 2.5 N=36	TioR 5 N=31
Age (years)			
Mean (SD)	3.2 (1.4)	3.1 (1.5)	3.1 (1.3)

Demographic Parameters	Placebo N=34	TioR 2.5 N=36	TioR 5 N=31
Median	4	3	3
Age groups, n (%)			
< 3 years	10 (29)	15 (42)	12 (39)
3 – 5 years	24 (71)	21 (58)	19 (63)
Gender, n (%)			
Female	13 (38)	17 (47)	10 (32)
Race, n (%)			
White	24 (71)	28 (78)	25 (81)
Black/African American	3 (9)	3 (8)	1 (3)
Asian	7 (21)	5 (14)	5 (16)
Ethnicity, n (%)			
Hispanic/Latino	0	0	0
Baseline lung function, pre-bronchodilator (mean)[1]			
	N=4	N=7	N=2
FEV_1 (L)	1.023	0.990	0.910
FVC (L)	1.123	1.201	1.075
FEV_1/FVC (%)	91	83	85
Medical History, n (%)			
Prematurity	2 (6)	4 (11)	2 (7)
Second hand smoke exposure	1 (3)	5 (14)	3 (10)
Atopic dermatitis/eczema	5 (15)	6 (17)	8 (26)
Food allergy	1 (3)	4 (11)	5 (16)
Allergic rhinitis/seasonal allergy	8 (24)	5 (14)	10 (32)
Asthma History (mean)			
Age at Onset (years)	1.8	1.4	1.5
Duration (years)	1.4	1.8	1.6
Concomitant Medications[2]			
Oral corticosteroids	2 (6)	3 (8)	4 (13)
LABA	8 (24)	6 (17)	6 (20)
Anticholinergics (short-acting)	2 (6)	2 (6)	1 (3)
Leukotriene modifiers	17 (50)	14 (39)	11 (36)
Xanthines	0	0	0
Omalizumab	0	0	0

[1]Measured at Visit 2
[2]Within 3 months of Visit 1
Source: CSR Tables 11.2.1:1, 15.1.4.1:1, 15.1.4.2:1, and 15.1.4.4:1 and MH dataset



The following table shows subject disposition; all randomized subjects completed the study.

Table 22. Subject Disposition: Study 443

	Placebo	TioR 2.5	TioR 5
Randomized	34	36	32
Treated, n (%)	34 (100)	36 (100)	31 (100)
Completed trial medication	34 (100)	36 (100)	31 (100)
Prematurely discontinued	0	0	0
Source: CSR 205.443, Table 10.1:1			

(b) (4)

(b) (4)

(b) (4)

(b) (4)

because these products are often used off-label with a spacer device in young patients, available clinical information in this age group, including in vitro characterization data with and without a spacer, is usually included in the product label.

7 Review of Safety

Safety Summary

This sNDA submission contains adequate data to support the safety of tiotropium Respimat 2.5 µg once daily for the long-term, once daily, maintenance treatment of asthma in patients 6 to 11 years of age. The evidence for safety in this population is based on a 12 and 48 week trial in 6 to 11 year old patients with severe and moderate asthma, respectively, and a 12 week trial in 1 to 5 year old patients with persistent asthma symptoms.

In this safety review, the 6 to 11 year old and 1 to 5 year old age groups were evaluated separately, and there were no major safety concerns or new safety signals identified in either population. In general, tiotropium Respimat demonstrated a similar safety profile in pediatric asthma patients to that observed in adults and adolescents with asthma. 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. With regard to drug-class specific safety concerns, reports of systemic anticholinergic effects, such as dry mouth, were rare.

Because these pediatric trials were initiated prior to approval of tiotropium Respimat 2.5 µg/day for adults and adolescents asthma (in contrast to 5 µg/day for COPD), both 2.5 µg and 5 µg once daily doses were evaluated in the three trials. Consistent with findings

in the adult and adolescent asthma development program, there was no evidence in the safety database to suggest that the higher 5 µg dose in this pediatric population is unsafe as there was no apparent difference in frequency or severity of adverse events between the two doses.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary safety database used to evaluate the safety of tiotropium Respimat in pediatric patients ages 1 to 11 years of age included 48 and 12 week trials in 6 to 11 year olds (445 and 446) as well as a 12 week trial in 1 to 5 year olds (443). All trials were similar in design (randomized, double-blind, parallel group) and evaluated two doses of tiotropium Respimat (2.5 and 5 µg daily).

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 signing of informed consent/assent until 21 days after the last dose of trial medication and followed until they had resolved or been sufficiently characterized. 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). Adverse events of special interest (AESI) were reports of hepatic injury meeting pre-specified criteria of AST/ALT elevations ≥ 3x ULN combined with total bilirubin elevation ≥ 2x ULN in the same sample. 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 Complete Study Reports (CSR) and Summary of Clinical Safety (SCS) were coded using MedDRA version 18.1. 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

This review analyzes pooled safety data from trials 445 and 446 in 6 to 11 year old patients and presents safety data from trial 443 in 1 to 5 year old patients separately.

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 6 to 11 year olds in controlled clinical trials to both doses of tiotropium Respimat is adequate for the safety evaluation of a drug intended for chronic use of a non-life-threatening disease.

Table 25. Exposure in 6 to 11 year olds: Studies 445 and 446

Extent of Exposure in Days, n (%)	Placebo (N=265)	TioR 2.5 (N=271)	TioR 5 (N=265)
1-28	4 (2)	0	1 (0.4)
29-56	0	0	0
57-112	130 (49)	136 (50)	129 (49)
113-168	4 (2)	4 (2)	0
169-224	2 (1)	0	1 (0.4)
225-280	1 (0.4)	1 (0.4)	1 (0.4)
281-336	46 (17.4)	51 (19)	53 (20)
337-363	73 (28)	79 (29)	78 (29)
≥365	5 (2)	0	1 (0.4)

N=Treated Set
Source: Module 5.3.5.3, SCS Supplement, Table 1.1, p2474

The extent and duration of exposure in 1 to 5 year old patients is limited; however, since a study in this age group was not specifically requested or required, any safety information gathered is considered beneficial.

Table 26. Exposure in 1 to 5 year olds

Extent of Exposure in Days, n (%)	Placebo (N=34)	TioR 2.5 (N=36)	TioR 5 (N=31)
1-29	0	0	0
30-56	0	0	0
57-84	7 (21)	12 (33)	10 (32)
≥85	27 (79)	24 (67)	21 (68)

N=Treated Set
Source: CSR 205.443, Table 12.1:1, p101

Patient demographics in the safety population of 6 to 11 year olds and 1 to 5 year olds were relatively similar among treatment groups (refer to Table 21 for demographics in 1

to 5 year olds). Overall, the safety population is predominantly white and male with relatively few black and Asian patients, but substantial numbers of American Indian/Alaskan Natives and Hispanics. In the 6 to 11 year old studies, the population skews toward the older end of the age range.

Table 27. Demographic Profile of the 6 to 11 year old Pooled Safety Population

Demographic Parameters	Placebo (N=265)	TioR 2.5 (N=271)	TioR 5 (N=265)	Total (N=801)
Age (years)				
Mean (SD)	9 (1.6)	9 (1.6)	9 (1.7)	9 (1.6)
Median	9	9	9	9
Age Groups				
6-8 years	98 (37)	113 (42)	95 (36)	306 (38)
9-11 years	167 (63)	158 (58)	170 (64)	495 (62)
Sex, n (%)				
Female	87 (33)	78 (29)	93 (35)	258 (32)
Race, n (%)				
White	233 (88)	235 (87)	229 (86)	697 (87)
Black	2 (1)	6 (2)	4 (2)	12 (2)
Asian	3 (1)	4 (2)	5 (2)	12 (2)
Hawaiian/Pacific Islander	0	0	0	0
American Indian/Alaskan Native	27 (10)	26 (10)	27 (10)	80 (10)
Ethnicity, n (%)				
Hispanic/Latino	46 (17)	41 (15)	40 (15)	127 (16)
Weight (kg)				
Mean (SD)	35 (11)	35 (10)	36 (10)	35 (10)
Range	16-78	16-76	18-82	16-82
Height (cm)				
Mean (SD)	139 (11)	139 (11)	140 (11)	139 (11)
Range	117-170	113-169	109-172	109-172
Duration of Asthma, n (%)				
< 1 year	15 (6)	9 (3)	12 (5)	36 (5)
1-3 years	54(20)	69 (26)	69 (26)	192 (24)
≥ 3 years	196 (74)	193 (71)	184 (69)	573 (72)

Abbreviations: TioR 2.5=Tiotropium Respimat 2.5 µg/day, TioR 5=Tiotropium Respimat 5 µg/day, SD=standard deviation
N=Treated Set from trials 445 and 446
Source, Module 5.3.5.3, SCS Supplement. Table 4.1.1, p91

7.2.2 Explorations for Dose Response

As in the adult and adolescent asthma development program, two doses of tiotropium Respimat, 2.5 and 5 µg daily, were evaluated in these trials.

Table 28. Total Person Time Exposure in the Overall Safety Population

Exposure	Number of Patients	Patient Years
1 to 11 year olds		
TioR 2.5	307	163.1
TioR 5	296	160.8

Exposure	Number of Patients	Patient Years
6 to 11 year olds		
TioR 2.5	271	154.7
TioR 5	265	153.6
1 to 5 year olds		
TioR 2.5	36	8.4
TioR 5	31	7.2

Abbreviations: TioR 2.5=Tiotropium Respimat 2.5 µg/day, TioR 5=Tiotropium Respimat 5 µg/day
Source: Module 5.3.5.3, SCS Supplement, Tables 1.3, 1.6, and 3.1, p2476, 2479, and 4514

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 (in 6 to 11 year olds only) at screening. The CBC included hemoglobin, hematocrit, erythrocyte count, leukocyte count and differential, total eosinophil count (baseline only), and platelet count. The serum chemistry included lactate dehydrogenase, alanine transaminase, γ-glutamyl-transferase, aspartate transaminase, glucose, sodium, chloride, potassium, calcium, phosphorus (443 only), creatinine (at baseline only in 445 and 446), and total serum immunoglobulin E (baseline only). Clinical labs were repeated at Visits 4 and 6 in Study 445 and Visit 5 in Studies 443 and 446. EKGs were repeated at the end of study (Visit 6 or 5), and urine pregnancy testing was performed throughout Studies 445 and 446. New abnormal findings (not present at baseline/screening) or worsening of baseline conditions at subsequent visits were recorded as AEs.

7.2.5 Metabolic, Clearance, and Interaction Workup

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.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported in this submission.

7.3.2 Nonfatal Serious Adverse Events

The majority of nonfatal SAEs occurred in the placebo group, including all reported cases of anaphylaxis. Equal numbers of hospitalizations due to asthma exacerbations occurred across all treatment groups.

Table 29. Nonfatal SAEs in 6 to 11 year olds: Studies 445 and 446

Unique Subject ID	Dictionary Derived Term	Study Day Start of AE	Study Day End of AE	Severity	Reason for Seriousness	Resolved or Recovered
Placebo						
0004451931	Gastroenteritis	238	243	MODERATE	Hospitalization	Y
0004452201	Renal abscess	56	71	MODERATE	Hospitalization	Y
0004452592	Asthma	109	123	MODERATE	Hospitalization	Y
0004452715	Asthma	62	68	MODERATE	Hospitalization	Y
0004452845	Concussion	63	121	SEVERE	Hospitalization	Y
	Fall	63	63	MILD	Hospitalization	Y
	Paranasal sinus hematoma	63	75	MILD	Hospitalization	Y
	Skull fracture	63	75	MODERATE	Hospitalization	Y
0004454301	Anaphylactic reaction	59	59	SEVERE	Medically Important	Y
	Anaphylactic reaction	70	70	SEVERE	Medically Important	Y
0004464153	Asthmatic crisis	68	72	SEVERE	Hospitalization	Y
0004465563	Asthma	18	34	MODERATE	Hospitalization	Y
TioR 2.5						
0004454042	Appendicitis	7	21	SEVERE	Hospitalization	Y
0004454581	Asthma	55	58	MODERATE	Hospitalization	Y
0004454631	Asthma	90	94	MODERATE	Hospitalization	Y
0004463554	Asthma	78	82	SEVERE	Hospitalization	Y
0004463672	Epilepsy	47	--	SEVERE	Medically Important	N
TioR 5						
0004454038	Appendicitis	69	83	SEVERE	Hospitalization	Y
	Ileus paralytic	75	79	SEVERE	Hospitalization	Y
0004461631	Asthma	54	57	SEVERE	Hospitalization	Y
0004461968	Asthma	72	83	SEVERE	Hospitalization	Y
0004462775	Asthma	78	141	MODERATE	Hospitalization	Y
0004463686	Appendicitis	77	78	SEVERE	Hospitalization	Y

Source: Reviewer generated table in JReview using POPU (POPUDC=TS, POPUNYDC=Y), AE (AESER=Y, AESTDY > 0) and GENTRT datasets.

7.3.3 Dropouts and/or Discontinuations

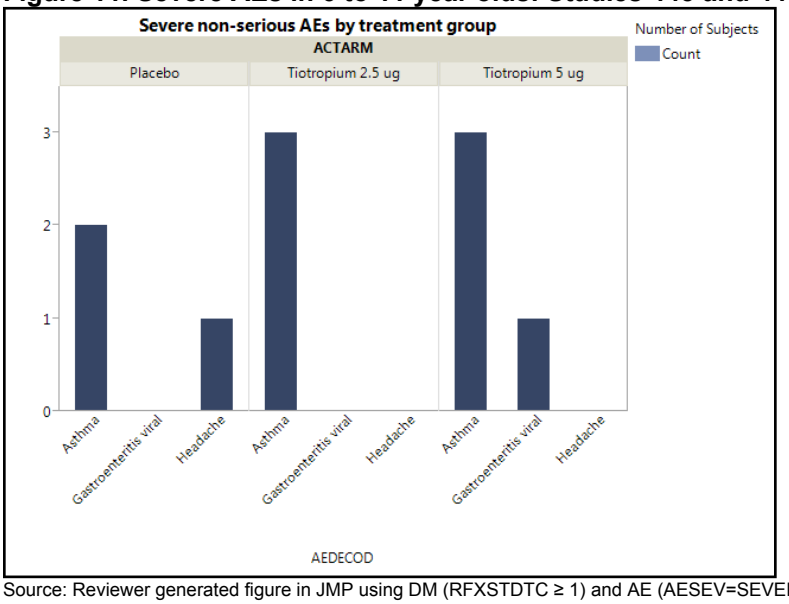
In Study 445, no subjects dropped out of the study prematurely due to an AE. Early dropouts were due to patient refusal to continue taking study medication/withdrawal of consent, relocating/moving (coded as other), and lost to follow up often as a result of

family emergency/death. In Study 446, dropouts due to an AE only occurred in the placebo group. Premature discontinuations coded as "other" were also due to moving away/changes in social situation.

7.3.4 Significant Adverse Events

Additional significant AEs that were categorized as severe and not already discussed in Sections 7.3.2 and 7.3.3 are shown in the figure below. The y-axis indicates number of subjects within each treatment arm; the x-axis indicates the severe, nonserious AE by MedDRA Preferred Term. Asthma was the most common, but the overall number of events was low and similar between treatment groups.

Figure 11. Severe AEs in 6 to 11 year olds: Studies 445 and 446



Source: Reviewer generated figure in JMP using DM (RFXSTDTC ≥ 1) and AE (AESEV=SEVERE, AESTDY ≥ 1, AESER=N) datasets

7.3.5 Submission Specific Primary Safety Concerns

Consistent with the data in adult/adolescent asthma and COPD patients, there was no pattern of AEs to suggest an increase in systemic anticholinergic effects associated with tiotropium Respimat treatment. There were no reports of dry mouth or urinary retention in the 6 to 11 year old age group.

7.3.6 Safety in 1 to 5 year old patients

The safety of TioR in 1 to 5 year old patients was generally similar to the safety profile observed in 6 to 11 year old patients. In Study 443, there were no deaths and no premature discontinuations. Three subjects in the placebo group experienced SAEs (appendicitis, viral URI, asthma and pneumonia) requiring hospitalization. No SAEs occurred in either tiotropium Respimat group. No severe TEAEs were reported, and the

overall number of moderate TEAEs was greatest in the placebo group. Common TEAEs shown in Table 31 revealed no new safety issues in this age group. Regarding potential anticholinergic class effects, events were rare with three reports of dry mouth (2 placebo, 1 TioR 5).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Treatment-emergent events occurring with a frequency of at least 2% in either TioR treatment group and with a greater frequency than placebo in 6 to 11 year olds are shown in the following table. With the exception of tonsillitis, which is more common in pediatric patients, all other common AEs are already listed in the product label. Notably, the frequency of asthma AEs in both tiotropium groups (26% each) was lower than compared to placebo (33%), and there were similar frequencies of decreased peak expiratory flow rates across all treatment groups (17%).

Table 30. Common TEAEs Occurring with Frequency ≥ 2% and Greater than Placebo in 6 to 11 year olds

MedDRA SOC	MedDRA PT[1]	Placebo N=265	TioR 2.5 N=271	TioR 5 N=265
Number of unique subjects with any TEAE, n (%)		**155 (59)**	**145 (54)**	**138 (52)**
Infections and infestations	Bronchitis	1 (0.4)	6 (2)	2 (1)
	Pharyngitis	7 (3)	10 (4)	2 (1)
	Tonsillitis, bacterial or streptococcal tonsillitis	5 (2)	9 (3)	2 (1)
	Viral infection	0	3 (1)	4 (2)
Nervous system disorders	Headache	6 (2)	8 (3)	2 (1)

Abbreviations:SOC=System Organ Class, PT=Preferred Term, TioR 2.5=tiotropium Respimat 2.5 µg/day, TioR 5=tiotropium Respimat 5 µg/day
N=Treated Set, n=number of subjects reporting the adverse event
[1]Related Preferred Terms have been combined
Reviewer generated table in JReview using DM (RFXSTDTC ≥ 1) and AE (AESTDY ≥ 1) datasets

Similarly in 1 to 5 year old patients, there were no new safety signals identified among the common TEAEs.

Table 31. Common TEAEs occurring in at least 3 Subjects and with greater frequency than placebo in 1 to 5 year old patients

MedDRA SOC	MedDRA PT[1]	Placebo N=34	TioR 2.5 N=36	TioR 5 N=31
Number of unique subjects with any TEAE, n (%)		**25 (74)**	**20 (56)**	**18 (58)**
Infections and infestations	Nasopharyngitis	5 (15)	7 (20)	2 (7)
	Upper respiratory tract infection, respiratory tract infection viral	5 (15)	6 (17)	8 (26)

	Rhinitis	3 (8)	2 (6)	3 (10)
Respiratory, thoracic and mediastinal disorders	Cough	3 (9)	4 (11)	2 (7)
	Rhinorrhea	3 (9)	0	3 (10)
	Nasal congestion	1 (3)	3 (8)	1 (3)
Nervous system disorders	Headache	0	2 (6)	1 (3)

Abbreviations:SOC=System Organ Class, PT=Preferred Term, TioR 2.5=tiotropium Respimat 2.5 µg/day, TioR 5=tiotropium Respimat 5 µg/day
N=Treated Set, n=number of subjects reporting the adverse event
[1]Related Preferred Terms have been combined
Source: CSR 205.443, Table 12.2.2:1

7.4.2 Laboratory Findings

There were no reports or observations of clinically meaningful differences in laboratory parameters between either tiotropium Respimat group and placebo. The only laboratory abnormality-related AEs occurred in Study 445: one patient in the TioR5 group had elevated AST and LDH of mild intensity (subject 4453012) and one patient in the TioR 2.5 group (subject 4455446) had a decreased neutrophil count of mild intensity; both recovered.

7.4.3 Vital Signs

No clinically meaningful effects on heart rate or blood pressure were noted during the treatment period in trials of either 6 to 11 year old or 1 to 5 year old patients. Additionally, no clinically significant differences in vital signs were observed with tiotropium Respimat treatment during trials for COPD or trials for asthma in adults and adolescents.

7.4.4 Electrocardiograms (ECGs)

No clinically significant changes in ECGs from baseline to end of treatment were identified in any of the trials. Furthermore, trials conducted with tiotropium Respimat for COPD and asthma in adults and adolescents 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

Significant adverse events (i.e., those that were serious, severe, or led to discontinuation) occurred with the same frequency in the TioR 2.5 and 5 µg dose groups and were rare overall. In addition, there was no dose dependency with regard to the frequency serious or non-serious of asthma-related AEs. Although anticholinergic-related AEs are known to increase with increasing doses, these types of AEs were rare in the 1 to 11 year old age group and provided no evidence of dose dependency in these trials.

7.5.2 Time Dependency for Adverse Events

There was no meaningful difference between treatment groups in time to first event for any particular AE.

7.5.3 Drug-Demographic Interactions

No substantial or consistent differences in AEs based on demographic factors such as sex, race, or ethnicity were observed although the absolute number of patients in some of the demographic subgroups was small.

7.5.4 Drug-Disease Interactions

No major differences in AEs based on asthma severity were identified.

7.5.5 Drug-Drug Interactions

No dedicated DDI studies were submitted. No major differences in AEs based on prior LABA use were observed.

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

Pregnancy testing was performed throughout studies 445 and 446; no pregnancies were reported in the 6 to 11 year old age group.

7.6.3 Pediatrics and Assessment of Effects on Growth

No growth studies were included in this submission as no growth effects are known or expected to occur with the use of tiotropium Respimat.

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 adult asthma development program, a maximum dose of TR 10 µg/day was evaluated; 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 TR for 3 weeks with no major safety issues.

7.7 Additional Submissions / Safety Issues

A safety update was submitted covering the period from March 1, 2016 through September 28, 2016. Since no clinical trials were recently completed or ongoing, BI provided additional postmarketing reports that were collected during this time period. During this time frame, there were 352 postmarketing case reports that included the indication term “asthma”, and of these nine were in patients less than 18 years of age. Only two reports were for children < 12 years of age. One was for a 4 year old female and reported that the drug was administered to a patient of inappropriate age. The other was for a 7 year old male in the US describing HandiHaler off-label use and cough.

8 Postmarket Experience

Through February 29, 2016, there were 5,048 individual case safety reports for Spiriva Respimat, Spiriva HandiHaler, or Spiriva Unassigned that included the term “asthma”. Of these, there were 11 reports in children 1 to 11 years of age: 8 in children 6 to 11 years and 3 in children 1 to 5 years. No new safety issues were identified that alter the risk/benefit assessment of tiotropium Respimat use in pediatric patients 6 to 11 years of age with asthma.

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 AND pediatric; no limits] yielded 12 references. The articles were reviewed briefly, and no new information was identified that changed the risk/benefit assessment in patients under 12 years of age.

9.2 Labeling Recommendations

Labeling discussions were ongoing at the time of this review; however, the major clinical revisions to the label are summarized below.

Section 1.2 Maintenance Treatment of Asthma: the proposed indication (b) (4) 6 years of age and older

Section 8.4 Pediatric Use: Data from Study 443 in 1 to 5 year old patients will be included here.

Section 14.2 Asthma: Results of the key secondary endpoint, trough FEV1, will be added from Studies 445 and 446 in 6 to 11 year old patients. (b) (4)

9.3 Advisory Committee Meeting

Tiotropium Respimat is commercially available for the treatment of asthma in patients 12 years of age and older as well as COPD. Because there were no significant efficacy or safety issues identified in the proposed pediatric population, the Pulmonary and Allergy Drug Advisory Committee (PADAC) was not convened for this application.

9.4 Additional Tables and Questionnaires from Study Protocols

Table 32. Timing of Assessments Relative to Study Drug Administration: Study 445

	Timing related to evening inhalation of study drug									
	-10h	-1h	-30'	-15'	-10'	0	30'	1h	2h	3h
Administration of questionnaires[1]		← ------ →								
Use of eDiary/ PEF-meter by the patient, Download , Review of data by investigator		← ------ →								
Urine pregnancy test[2,3]	← ---------- →									
Laboratory testing[3]	← ---------- →									
12-lead ECG[3,4]	← ---------- →									
Administer patient's usual asthma medication followed by trial medication[5]						X				
Vital signs (seated)[6]					X		X	X	X	X
Pulmonary function test[7]					X		X	X	X	X

1. Questionnaires will be administered at the beginning of the visit and should precede any discussion with a health professional.
2. Urine pregnancy testing only for all postmenarchal girls.
3. Urine pregnancy testing, laboratory testing and 12-lead ECG (during the treatment period laboratory tests and ECG are required only at Visit 6/EoT) may occur before administration of questionnaires if completion in the afternoon/evening is not possible, under condition that questionnaires administration occurs before any discussion with a health professional.
4. A 12-lead ECG will be recorded prior to vital signs, with the patient supine and rested for a minimum of 5 minutes. See Section 5.2.4 for further instructions.
5. Administration of trial medication will occur between 4:00 p.m. and 7:00 p.m. at Visit 2 and within ± 30 minutes of time of administration at Visit 2 at any following visits during the treatment period. Administration sequence: 1. patient's usual iCS (if regular posology); 2. patient's usual other controller medication (if any); 3. trial medication from Respimat®. Time point zero is defined as the time of complete inhalation (i.e. end time of second inhalation from Respimat®).
6. Vital signs (pulse rate and blood pressure) will be measured immediately before pulmonary function testing, with the patient seated and rested for a minimum of 5 minutes. See Section 5.2.5 for further instructions.
7. The 10 minute pre-dose measurement will be obtained in the period from 25 minutes to 5 minutes prior to the evening dose of study medication. The 30 and 60 minute measurements will be obtained within ± 5 minutes of the specified time point; measurements made at 2 and 3 hours post-dose will be performed within ± 10 minutes of the scheduled time point. Post-dose measurements will be done at Visits 2, 4 and 6 only.

Source: CTP 205.445 version 3.0, p8

Figure 12. Interviewer-Administered Asthma Control Questionnaire (ACQ-IA)

First, read each question to the child using the primary wording. If the child does not fully understand the question, read it again using the secondary wording shown in brackets (e.g. 2a, 3a etc.).

1. During the past week, how often were you **woken by your asthma** during the night?

2. During the past week, how **bad were your asthma symptoms when you woke up** in the morning?

2a During the past week, how **bad were your asthma symptoms (for instance, hard to breath, wheeze, cough) when you woke up** in the morning?)

3. During the past week, how **limited were you in your activities** because of your asthma?

3a During the past week, how **bothered were you in the things you do every day** because of your asthma?)

4. During the past week, how much **shortness of breath** did you experience because of your asthma?

4a During the past week, how much **shortness of breath (hard or difficult to breath, breathless)** did you have because of your asthma?)

5. During the past week, how much time did you **wheeze?**

6. During the past week, how many **puffs of short-acting bronchodilator** (your **Reliever** puffer e.g. Ventolin/Bricanyl) have you used each day?

6a During the past week, how many **puffs of your Reliever (quick relief, rescue)** asthma medicine have you used each day?)

RESPONSE SHEET

Question	Response (0-6)
1. Woken by asthma	.....
2. Asthma symptoms on waking	.....
3. Activity limitation	.....
4. Short of breath	.....
5. Wheeze	.....
6. Bronchodilator	.....

Please circle the response (0-6) for the child's FEV_1% predicted

7.	FEV_1pre-bronchodilator:	0	> 95% predicted
		1	95 - 90%
	FEV_1predicted:.....	2	89 - 80%
		3	79 - 70%
	FEV_1%predicted:.....	4	69 - 60%
	(Record actual values on the dotted lines and score the FEV_1% predicted in the next column)	5	59 - 50%
		6	< 50% predicted

Source: Clinical trial protocol, 205.445, Appendix 10.5, p122

Figure 13. Pediatric Asthma Quality of Life Questionnaire with Standardized Activities (PAQLQ(S))

I want you to tell me how much you have been bothered by your asthma during the past week. I will tell you which card to use. Pick the number that best describes how much you were bothered by your asthma during the past week.

A	1.	How much have you been bothered by your asthma in **PHYSICAL ACTIVITIES** (such as running, swimming, sports, walking uphill/upstairs and bicycling) during the past week? [BLUE CARD]
A	2.	How much have you been bothered by your asthma in **BEING WITH ANIMALS** (such as playing with pets and looking after animals) during the past week? [BLUE CARD]
A	3.	How much have you been bothered by your asthma in **ACTIVITIES WITH FRIENDS AND FAMILY** (such as playing at recess and doing things with your friends and family) during the past week? [BLUE CARD]
S	4.	How much did **COUGHING** bother you in the past week? [BLUE CARD]
E	5.	How often did your asthma make you feel **FRUSTRATED** during the past week? [GREEN CARD]
S	6.	How often did your asthma make you feel **TIRED** during the past week? [GREEN CARD]
E	7.	How often did you feel **WORRIED, CONCERNED, OR TROUBLED** because of your asthma during the past week? [GREEN CARD]
S	8.	How much did **ASTHMA ATTACKS** bother you during the past week? [BLUE CARD]
E	9.	How often did your asthma make you feel **ANGRY** during the past week? [GREEN CARD]
S	10.	How much did **WHEEZING** bother you during the past week? [BLUE CARD]
E	11.	How often did your asthma make you feel **IRRITABLE (cranky, grouchy*)** during the past week? [GREEN CARD] (*use only if patient does not understand the word "irritable")
S	12.	How much did **TIGHTNESS IN YOUR CHEST** bother you during the past week? [BLUE CARD]
E	13.	How often did you feel **DIFFERENT OR LEFT OUT** because of your asthma during the past week? [GREEN CARD]
S	14.	How much did **SHORTNESS OF BREATH** bother you during the past week? [BLUE CARD]
E	15.	How often did you feel **FRUSTRATED BECAUSE YOU COULDN'T KEEP UP WITH OTHERS** during the past week? [GREEN CARD]
S	16.	How often did your asthma **WAKE YOU UP DURING THE NIGHT** during the past week? [GREEN CARD]
E	17.	How often did you feel **UNCOMFORTABLE** because of your asthma during the past week? [GREEN CARD]
S	18.	How often did you feel **OUT OF BREATH** during the past week? [GREEN CARD]
A	19.	How often did you feel **YOU COULDN'T KEEP UP WITH OTHERS** because of your asthma during the past week? [GREEN CARD]
S	20.	How often did you have trouble **SLEEPING AT NIGHT**, because of your asthma, during the past week? [GREEN CARD]
E	21.	How often did you feel **FRIGHTENED BY AN ASTHMA ATTACK** during the past week? [GREEN CARD]
A	22.	Think about all the activities that you did in the past week. How much were you bothered by your asthma doing these activities? [BLUE CARD]
S	23.	How often did you have difficulty taking a **DEEP BREATH** in the past week? [GREEN CARD]

DOMAIN CODE:

S = Symptoms
A = Activity Limitation
E = Emotional Function

RESPONSE OPTIONS

GREEN CARD

1. ALL OF THE TIME
2. MOST OF THE TIME
3. QUITE OFTEN
4. SOME OF THE TIME
5. ONCE IN A WHILE
6. HARDLY ANY OF THE TIME
7. NONE OF THE TIME

BLUE CARD

1. EXTREMELY BOTHERED
2. VERY BOTHERED
3. QUITE BOTHERED
4. SOMEWHAT BOTHERED
5. BOTHERED A BIT
6. HARDLY BOTHERED AT ALL
7. NOT BOTHERED

Source: Clinical Trial Protocol, Appendix 10.6, p127

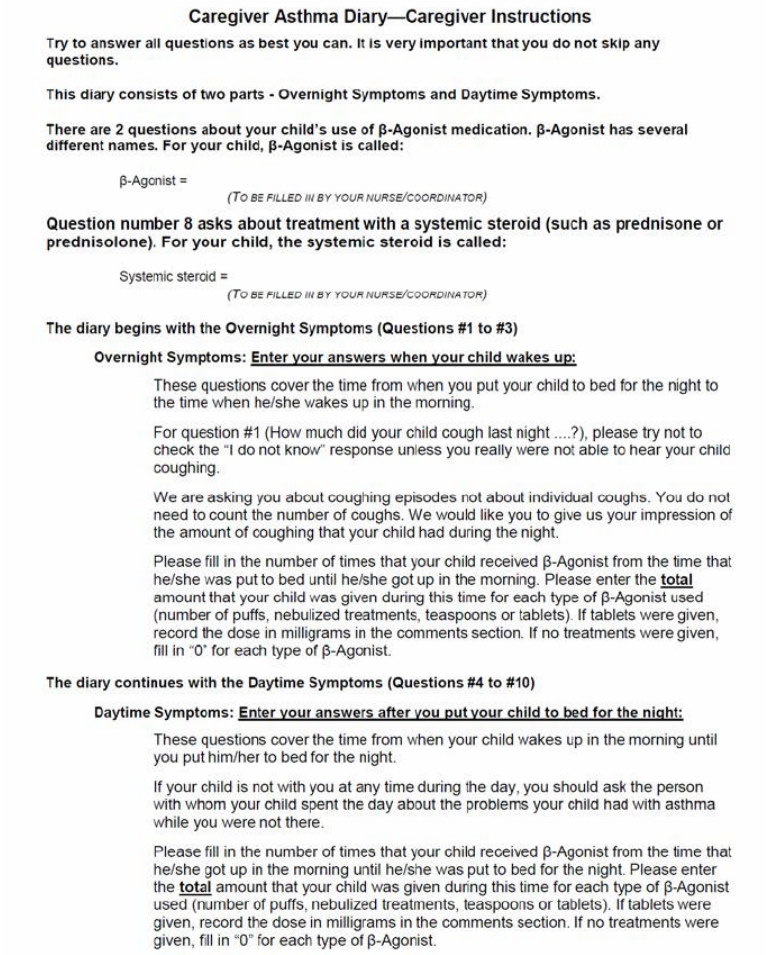
Table 33. Timing of assessments relative to study drug administration: Study 443

	Timing related to inhalation of study medication						
hrs / min.	-1h	-10'	0	30'	1h	2h	3h
Assessment of asthma control[2]	←.....→						
Caregiver's global impression of change (CGI-C)[3]	←.....→						
Vital signs[3, 5]	←.....→						
ECG[3,5]	←.....→						
Physical exam[4]	←.....→						
Laboratory testing[4]	←.....→						
Inhalation of medication[6]			X				
PK urine collection[7]	X			←.....→			←.....→
PFT[8]		X		X	X	X	X
Rint[9]		X		X			
IOS[9]		X		X			

1. Pharmacokinetics (PK): Only applicable to subset (and only after signing informed consent/assent for PK).
   PFT: Only applicable to 5 year olds capable of providing PFTs of acceptable quality.
   Rint /IOS: Optional and only applicable to 2-5 year olds capable of providing Rint / IOS measurements of acceptable quality (with a mouthpiece). Not applicable to 5 year old patients capable of providing PFTs of acceptable quality.
2. Visit 2 only and prior to PFT/Rint /IOS (if applicable).
3. Vital signs at all visits, but at Visits 2 and 5 prior to PFT/Rint/IOS (if applicable). The CGI-C should be completed at Visit 5 only and prior to other visit assessments and should precede any discussions with a health professional (physician, nurse or study co-ordinator).
4. Visit 5 only.
5. To be obtained with patient rested for a minimum of 5 minutes.
6. Study medication should be administered as described in Section 4.1.4. Time point zero is defined as the end of inhalation from the Respimat®.
7. Refer to Section 5.5.2 and lab manual for instructions. Pre-dose sample: 1 sample collected within the hour pre-dose. Post-dose samples: all urine voided during the interval should be collected.
8. Pulmonary function tests should always be performed as close to the given time point as possible.
9. Rint and IOS measurements should always be performed as close to the given time point as possible.

Source: Clinical trial protocol 205.443, p7

Figure 14. Pediatric Asthma Caregiver Diary (PACD), Study 443



Caregiver Asthma Diary—Caregiver Instructions

Try to answer all questions as best you can. It is very important that you do not skip any questions.

This diary consists of two parts - Overnight Symptoms and Daytime Symptoms.

There are 2 questions about your child's use of β-Agonist medication. β-Agonist has several different names. For your child, β-Agonist is called:

β-Agonist =
(TO BE FILLED IN BY YOUR NURSE/COORDINATOR)

Question number 8 asks about treatment with a systemic steroid (such as prednisone or prednisolone). For your child, the systemic steroid is called:

Systemic steroid =
(TO BE FILLED IN BY YOUR NURSE/COORDINATOR)

The diary begins with the Overnight Symptoms (Questions #1 to #3)

Overnight Symptoms: Enter your answers when your child wakes up:

These questions cover the time from when you put your child to bed for the night to the time when he/she wakes up in the morning.

For question #1 (How much did your child cough last night ....?), please try not to check the "I do not know" response unless you really were not able to hear your child coughing.

We are asking you about coughing episodes not about individual coughs. You do not need to count the number of coughs. We would like you to give us your impression of the amount of coughing that your child had during the night.

Please fill in the number of times that your child received β-Agonist from the time that he/she was put to bed until he/she got up in the morning. Please enter the **total** amount that your child was given during this time for each type of β-Agonist used (number of puffs, nebulized treatments, teaspoons or tablets). If tablets were given, record the dose in milligrams in the comments section. If no treatments were given, fill in "0" for each type of β-Agonist.

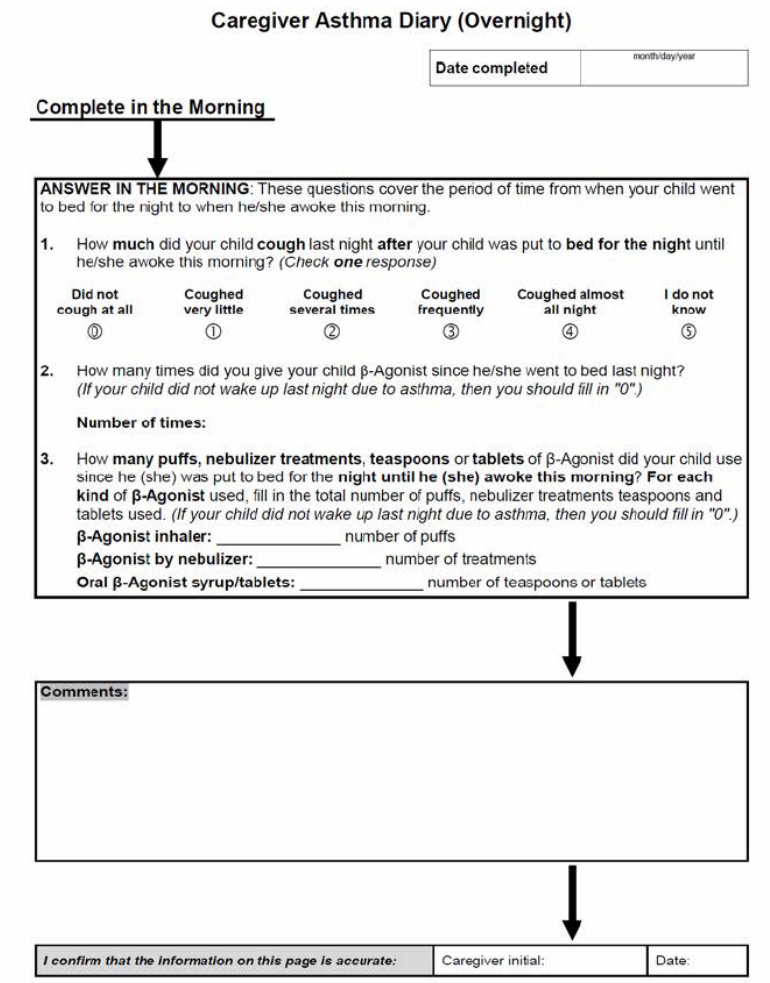
The diary continues with the Daytime Symptoms (Questions #4 to #10)

Daytime Symptoms: Enter your answers after you put your child to bed for the night:

These questions cover the time from when your child wakes up in the morning until you put him/her to bed for the night.

If your child is not with you at any time during the day, you should ask the person with whom your child spent the day about the problems your child had with asthma while you were not there.

Please fill in the number of times that your child received β-Agonist from the time that he/she got up in the morning until he/she was put to bed for the night. Please enter the **total** amount that your child was given during this time for each type of β-Agonist used (number of puffs, nebulized treatments, teaspoons or tablets). If tablets were given, record the dose in milligrams in the comments section. If no treatments were given, fill in "0" for each type of β-Agonist.



Caregiver Asthma Diary (Overnight)

Date completed	month/day/year

Complete in the Morning

ANSWER IN THE MORNING: These questions cover the period of time from when your child went to bed for the night to when he/she awoke this morning.

1. How **much** did your child **cough** last night **after** your child was put to **bed for the night** until he/she awoke this morning? *(Check **one** response)*

Did not cough at all	Coughed very little	Coughed several times	Coughed frequently	Coughed almost all night	I do not know
⓪	①	②	③	④	⑤

2. How many times did you give your child β-Agonist since he/she went to bed last night? *(If your child did not wake up last night due to asthma, then you should fill in "0".)*

   Number of times:

3. How **many puffs, nebulizer treatments**, **teaspoons** or **tablets** of β-Agonist did your child use since he (she) was put to bed for the **night until he (she) awoke this morning**? **For each kind** of **β-Agonist** used, fill in the total number of puffs, nebulizer treatments teaspoons and tablets used. *(If your child did not wake up last night due to asthma, then you should fill in "0".)*

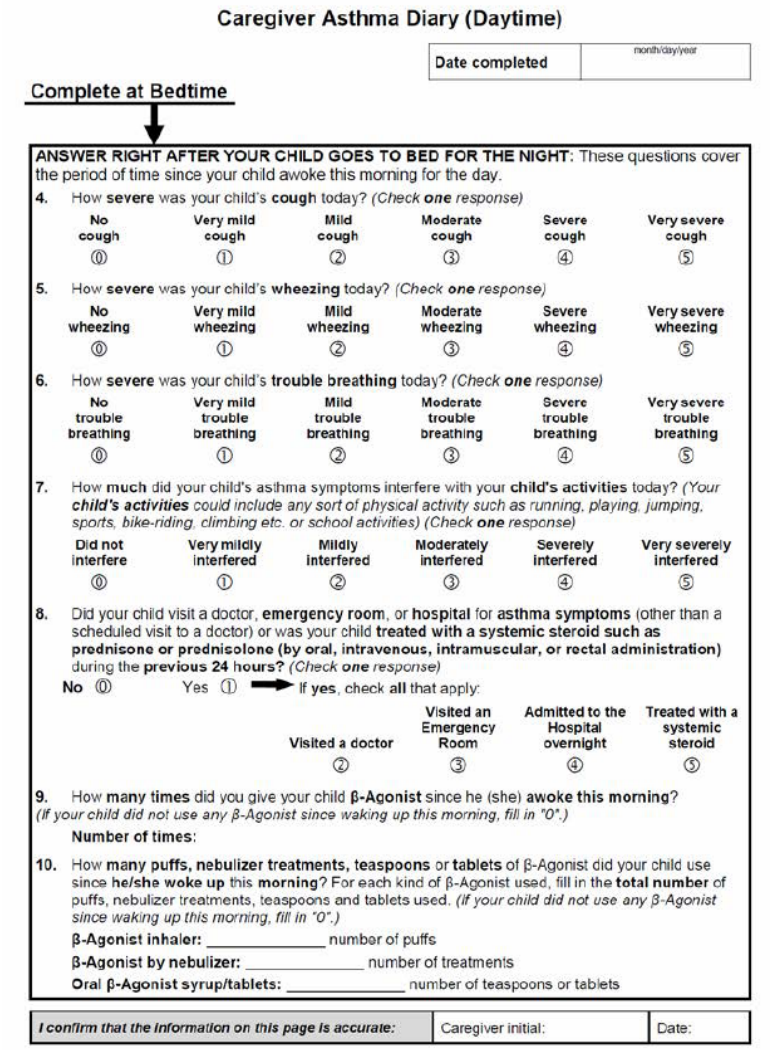
   β-Agonist inhaler: _____ number of puffs

   β-Agonist by nebulizer: _____ number of treatments

   Oral β-Agonist syrup/tablets: _____ number of teaspoons or tablets

Comments:

I confirm that the information on this page is accurate:	Caregiver initial:	Date:



Caregiver Asthma Diary (Daytime)

Date completed	month/day/year

Complete at Bedtime

ANSWER RIGHT AFTER YOUR CHILD GOES TO BED FOR THE NIGHT: These questions cover the period of time since your child awoke this morning for the day.

4. How **severe** was your child's **cough** today? *(Check **one** response)*

No cough	Very mild cough	Mild cough	Moderate cough	Severe cough	Very severe cough
⓪	①	②	③	④	⑤

5. How **severe** was your child's **wheezing** today? *(Check **one** response)*

No wheezing	Very mild wheezing	Mild wheezing	Moderate wheezing	Severe wheezing	Very severe wheezing
⓪	①	②	③	④	⑤

6. How **severe** was your child's **trouble breathing** today? *(Check **one** response)*

No trouble breathing	Very mild trouble breathing	Mild trouble breathing	Moderate trouble breathing	Severe trouble breathing	Very severe trouble breathing
⓪	①	②	③	④	⑤

7. How **much** did your child's asthma symptoms interfere with your **child's activities** today? *(Your **child's activities** could include any sort of physical activity such as running, playing, jumping, sports, bike-riding, climbing etc. or school activities) (Check **one** response)*

Did not interfere	Very mildly interfered	Mildly interfered	Moderately interfered	Severely interfered	Very severely interfered
⓪	①	②	③	④	⑤

8. Did your child visit a doctor, **emergency room**, or **hospital** for **asthma symptoms** (other than a scheduled visit to a doctor) or was your child **treated with a systemic steroid such as prednisone or prednisolone (by oral, intravenous, intramuscular, or rectal administration)** during the **previous 24 hours?** *(Check **one** response)*

No ⓪ Yes ① → If **yes**, check **all** that apply:

Visited a doctor	Visited an Emergency Room	Admitted to the Hospital overnight	Treated with a systemic steroid
②	③	④	⑤

9. How **many times** did you give your child **β-Agonist** since he (she) **awoke this morning**? *(If your child did not use any β-Agonist since waking up this morning, fill in "0".)*

Number of times:

10. How **many puffs, nebulizer treatments, teaspoons** or **tablets** of β-Agonist did your child use since **he/she woke up** this **morning**? For each kind of β-Agonist used, fill in the **total number** of puffs, nebulizer treatments, teaspoons and tablets used. *(If your child did not use any β-Agonist since waking up this morning, fill in "0".)*

β-Agonist inhaler: _____ number of puffs

β-Agonist by nebulizer: _____ number of treatments

Oral β-Agonist syrup/tablets: _____ number of teaspoons or tablets

I confirm that the information on this page is accurate:	Caregiver initial:	Date:

Source: Clinical Trial Protocol 205.443, Appendix 10.5, p107

Figure 15. Additional Diary Card: Study 443

Boehringer Ingelheim

TIOTROPIUM
Asthma
Treatment Period

Page 1

BI Trial No. 205.443 Visit: _____ Patient No.: _____

DIARY CARD

Dear parent/caregiver,

Please answer the following questions each morning and after answering the questions of the Caregiver Asthma Diary:
(please tick the appropriate box below)

	Did your child wake up during the night due to his/her asthma?					Did your child take his/her study drug yesterday afternoon from the Respimat® inhaler?	
Date completed	Did not wake up	Woke up once	Woke up 2–5 times	Woke up more than 5 times	Was awake all night	Yes	No
____/____/_____	o	o	o	o	o	o	o
____/____/_____	o	o	o	o	o	o	o
____/____/_____	o	o	o	o	o	o	o
____/____/_____	o	o	o	o	o	o	o
____/____/_____	o	o	o	o	o	o	o
____/____/_____	o	o	o	o	o	o	o
____/____/_____	o	o	o	o	o	o	o
____/____/_____	o	o	o	o	o	o	o
____/____/_____	o	o	o	o	o	o	o
____/____/_____	o	o	o	o	o	o	o
____/____/_____	o	o	o	o	o	o	o
____/____/_____	o	o	o	o	o	o	o
____/____/_____	o	o	o	o	o	o	o
____/____/_____	o	o	o	o	o	o	o
____/____/_____	o	o	o	o	o	o	o
____/____/_____	o	o	o	o	o	o	o
____/____/_____	o	o	o	o	o	o	o

Please continue on reverse side.

Source: Clinical Trial Protocol 205.443, Appendix 10.6, p110

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STACY J CHIN
01/18/2017

ANTHONY G DURMOWICZ
01/18/2017