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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review

CLINICAL STUDIES

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1 EXECUTIVE SUMMARY

The present submission provides results from three randomized, double blind, parallel arm trials, 0205-443 (study 443), 0205-445 (study 445), and 0205-446 (study 446), and one randomized, incomplete crossover trial, 0205-425 (study 425), to evaluate the efficacy of Spiriva Respimat (tiotropium) for the treatment of asthma in pediatric patients.

Studies 425, 445, and 446, were conducted in 6 to 11 year olds. Studies 425 and 445 enrolled patients with moderate persistent asthma, and study 446 enrolled patients with severe persistent asthma, All three studies included tiotropium 5mcg/day (T5), tiotropium 2.5 mcg/day (T2.5), and placebo (Pbo). In addition, study 425 included tiotropium 1.25 mcg/day (T1.25).

In trials 425 and 445, conducted in patients with moderate persistent asthma, T2.5, the approved dose for asthma in adolescent and adult patients, was superior to placebo for the primary endpoint, change from baseline peak $FEV_{1,0\text{-}3hr}$, and for the key secondary endpoint, change from baseline trough FEV_1.

However, in trial 446, which enrolled patients with severe rather than moderate asthma, there was no significant difference between T2.5 and Pbo for the primary and secondary endpoints. T5, however, was significantly superior to placebo. Several possible explanations for the lack of T2.5 efficacy in study 446 were evaluated: (i) Time of evaluation; in study 446, endpoints were measured at week 12, while study 445 endpoints were measured at week 24, suggesting that study 446 was not conducted for an adequate time to achieve treatment effects. However, in crossover study 425, significant treatment effects were achieved by week 4; (ii) Type 2 error; it is possible that a real treatment effect of T2.5 was missed due to random chance in study 446, however this possibility cannot be reliably evaluated; (iii) Greater use of long acting beta-2 agonists (LABA) in study 446; while more patients used LABA in study 446 than in the other two studies, within study 446 comparisons between patients on or off LABA showed no significant differences, with a p-value of .14 for LABA by treatment interaction. The point estimate for the difference between T2.5 and Pbo at week 12 was equal to 0.061 liters (95% CI: -0.079, 0.202) for patients not administered concurrent LABA and was equal to 0.022 liters (95% CI: -0.049, 0.094) for patients administered LABA; and (iv) Asthma severity; that trial 446 alone enrolled patients with severe persistent asthma rather than patients with moderate persistent asthma suggests that, to achieve an effect, patients with severe persistent asthma may require larger doses than patients with moderate persistent asthma. The medical team will consider the results of study 446 and prior studies of Spiriva Respimat when deciding on the final approved pediatric dose or indication.

Despite superiority for the primary and key secondary pulmonary function test endpoints, none of the three trials in six to eleven year-olds showed significant effects on patient-reported or caretaker-reported outcomes such as interviewer administered asthma control questionnaire, standardized pediatric asthma quality of life questionnaire, or change from baseline asthma symptom score.

(b) (4)

In conclusion, for 6 to 11 year olds who have moderate persistent asthma, this submission provides substantial evidence of effectiveness for T2.5, the dosage approved for asthma in adults and adolescents. For 6 to 11 year olds who have severe persistent asthma, it seems possible that a higher dose, T5, may be required to achieve a treatment effect. (b) (4)

2 INTRODUCTION

2.1 Overview

2.1.1 Drug Class and Indication

Spiriva Respimat (tiotropium), a long-acting anticholinergic, is currently approved for the treatment of COPD and for the treatment of asthma in patients 12 years of age and older.

2.1.2 History of Drug Development

Spiriva Respimat was approved under NDA 207070 by FDA on September 16, 2015 for the maintenance treatment of asthma in patients 12 years of age and older. On February 12, 2016, the Division requested that the sponsor submit to NDA 021936 results from Spiriva trials on pediatric asthma patients. This submission is in response to the February 12, 2016 pediatric written request.

2.1.3 Data Sources

Data sources for the current review are located at

\\cdsesub1\evsprod\NDA021936\0044\m5\datasets

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Datasets, programs, and documentation provided by the applicant were adequate to evaluate the proposed claims. Results from review analyses generally matched those provided in the submission.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The present submission provides results from three randomized, double blind, parallel arm trials and one randomized, incomplete crossover trial to evaluate the efficacy of tiotropium for the treatment of asthma in pediatric patients.

Double-blind, parallel-group, 48-week study 445 (Table 1) randomized 401 patients 6 to 11 years old with moderate asthma in a 1:1:1 ratio to T5, T2.5, or placebo Pbo delivered via the Respimat inhaler as an add-on to inhaled corticosteroids (ICS) and controller medications. The primary endpoint was peak $FEV_{1,0\text{-}3hr}$ at W24. The key secondary endpoint was trough FEV_1.

Double-blind, parallel-group, 12-week study 446 (Table 2) randomized 400 patients 6 to 11 years old with severe asthma in a 1:1:1 ratio to T5, T2.5, or Pbo, delivered via the Respimat inhaler as add-on to ICS and controller medications. The primary endpoint was peak $FEV_{1,0\text{-}3hr}$ at W12. The key secondary endpoint was trough FEV_1 at W12.

Double-blind, incomplete-crossover study 425 (Table 3) randomized 301 patients 6 to 11 years old with moderate persistent asthma in a 1:1:1:1 ratio to T1.25, T2.5, T5, or Pbo, delivered via the Respimat inhaler as add-on to ICS plus optional LABA or leukotriene. The trial was conducted in three four-week periods with no washout between periods. The primary endpoint was peak $FEV_{1,0\text{-}3hr}$.

Double-blind, parallel-group, 12-week study 443 (Table 4) randomized 101 patients 1 to 5 years old with severe asthma in a 1:1:1 ratio to T5, T2.5, or Pbo, delivered via the Respimat inhaler with or without a spacer (Aerochamber Plus Flow-Vu) as add-on to ICS. The primary endpoint was peak $FEV_{1,0\text{-}3hr}$ at W12. The key secondary endpoint was asthma symptom score at W12.

A variety of other secondary endpoints were evaluated in these studies, including additional spirometry-based endpoints and several patient-reported outcome measures.

Table 1. Designs for Study 445

Study	Design	Population	Endpoints
445	T5	Moderate persistent asthma	*Primary:*
	T2.5	Age 6 to 11 years	Peak $FEV_{1,0\text{-}3hr}$ W24
P2	Pbo	ACQ-IA ≥ 1.5	
		60% ≤ FEV_1 ≤ 90% pred	*Key Secondary:*
	+SOC	FEV_1 variation ≤ 30%	Trough FEV_1 W24, W48
		FEV_1 reversibility ≥ 12%	
	R, DB, PG		*Other Secondary:*
		On SOC before screening:	FVC $peak_{0\text{-}3hr}$ W24, W48
	End W48	medium dose ICS +/-	FVC trough W24, W48
		controller med	FEV_1 ($AUC_{0\text{-}3hr}$) W24
			FVC ($AUC_{0\text{-}3hr}$) W24
		Exclusions: recent	ACQ IA W24, W48
		acute exacerbations	PAQLQ(S) W24, W48
		≥ 6 rescue med / day	PRN rescue med W24, W48
		LAMA	PEF am/pm resp W24, W48
		theophylline	FEV_1 am/pm resp W24, W48
		systemic OCS	PEF var resp W24, W48
			Asthma symptoms W24, W48
		Prohibited: LABA	Time to first exacerbation[1]
		N = 135/135/131	
		Strat: country	

source: reviewer

P2 phase 2, T5 5 mcg inhaled tiotropium Q1D, T2.5 2.5 mcg inhaled tiotropium Q1D, or Pbo inhaled placebo Q1D SOC standard of care, R randomized, DB double blind, PG parallel-group, W48 week 48, ACQ-IA interviewer administered asthma control questionnaire, FEV_1 forced one-second expiratory volume, ICS inhaled corticosteroids, LAMA long acting muscarinic antagonist, OCS oral corticosteroids, LABA long acting beta-2 agonist, W24 week 24, FVC forced vital capacity, AUC area under curve, PAQLQ(S) standardized pediatric asthma quality of life questionnaire , rescue med albuterol, PRN as needed, PEF peak expiratory flow

[1] The onset of asthma exacerbation: the first worsened symptom or PEF deterioration. The end of an asthma exacerbation was defined by the investigator.

Table 2. Design for Study 446

Study	Design	Population	Endpoints
446	T5	Severe persistent asthma	*Primary (W12):*
	T2.5	Age 6 to 11 years	Peak $FEV_{1,0\text{-}3hr}$
P3	Pbo	ACQ-IA ≥ 1.5	
		60% ≤ FEV_1 ≤ 90% pred	*Key Secondary (W12):*
	+SOC	FEV_1 variation ≤ 30%	Trough FEV_1
		FEV_1 reversibility ≥ 12%	
	R, DB, PG		*Other Secondary (W12):*
		On SOC before screening:	FVC $peak_{0\text{-}3hr}$
	End W12	high dose ICS +	FVC trough
		controller med	FEV_1 ($AUC_{0\text{-}3hr}$)
		or	FVC ($AUC_{0\text{-}3hr}$)
		medium dose ICS +	ACQ IA
		2 controller med	PRN rescue med
			PEF am/pm resp
		Exclusions: recent	FEV_1 am/pm resp
		acute exacerbations	PEF var resp
		≥ 6 rescue med / day	Asthma symptoms
		LAMA	Time to first exacerbation
		theophylline	
		systemic OCS	
		Prohibited: LABA	
		N = 130/136/134	
		Strat: country	

source: reviewer

P3 phase 3, W12 week 12

Table 3. Design for Study 425

Study	Design	Population	Endpoints
425	T5	Moderate persistent asthma	*Primary:*
	T2.5	Age 6 to 11 years	Peak $FEV_{1,0\text{-}3hr}$
P2	T1.25	ACQ-IA ≥ 1.5	
	Pbo	60% ≤ FEV_1 ≤ 90% pred	*Secondary:*
		FEV_1 variation ≤ 30%	Trough FEV_1
	+SOC	FEV_1 reversibility ≥ 12%	FVC $peak_{0\text{-}3hr}$
			Trough FVC
	R, DB, IXO	On SOC:	FEV_1 ($AUC_{0\text{-}3hr}$)
		medium dose ICS +	FVC ($AUC_{0\text{-}3hr}$)
	3x4W trt periods	LABA (optional) or	PEF am/pm resp
	no washout	leukotriene mod (optional)	PRN rescue med
			ACQ IA
		Exclusions: recent	FEV_1 am/pm resp
		acute exacerbations	$FEF_{25\text{-}75\%}$
		LAMA	PEF variability
		theophylline	PAQLQ(S)
		systemic OCS	
		Prohibited: LABA	
		N = 76/74/75/76	

source: reviewer

IXO Incomplete crossover, mod modifier

Table 4. Design for Study 443

Study	Design	Population	Endpoints
443	T5	Persistent asthma	*Primary W12:*
	T2.5	Age 1 to 5 years	Asthma symptom score (day)
P2/3	Pbo	$FEV_1 \leq$ 90% pred	
		Partially controlled asthma	*Secondary:*
	+ICS		Asthma symptom score (night)
		On ICS	% days without asthma symptoms
	R DB, PG		
		Exclusions: recent	PRN rescue med
	12W	acute exacerbations	
		$\geq$ 6 rescue med / day	(capable 5 year olds)
			Trough FEV_1
		N = 31/36/34	FVC $peak_{0\text{-}3hr}$
			Trough FVC
			FEV_1 ($AUC_{0\text{-}3hr}$)
			FVC ($AUC_{0\text{-}3hr}$)

source: reviewer

3.2.2 Statistical Methodologies

3.2.2.1 Studies 445 and 446

Endpoints for studies 445 and 446 were analyzed using mixed model repeated measures (MMRM). The model included fixed effects treatment, country, visit and treatment-by-visit interaction, fixed covariates baseline value and baseline value-by-visit interaction, and patient as a random effect. Statistical tests were conducted on all treated patients at the two-sided 0.05 level of significance using Kenward-Rogers degrees of freedom. For pulmonary function test endpoints, except for use of last observation carried forward for missing serial post-dose measurements within visits, only observed data was used for the analysis.

In study 445, for ACQ-IA and for in-clinic pulmonary function tests, a spatial power covariance matrix for unequally spaced visits was used for within-patient variation. For eDiary, PALQ(S), and spirometry data collected using the AM3 device, a first order autoregressive AR(1) covariance matrix was used.

In study 446, for all endpoints, an AR(1) covariance matrix was used to model within-patient variability.

Type 1 error was controlled only over the primary and key secondary endpoints, analyzed in sequence. For each endpoint, T5 was first tested against placebo and, if significant, T2.5 was tested against placebo.

3.2.2.2 Study 425

Endpoints for study 425 were analyzed using MMRM with treatment, period, and baseline value as fixed effects and with patient as a random effect, with a compound symmetric (CS) covariance structure for within-patient variability. Where analyses failed to converge, a first order autoregressive (AR-1) structure was used. Statistical tests were conducted at the two-sided 0.05 level of significance using Kenward-Rogers degrees of freedom. For pulmonary function test endpoints, post-dosing data missing due to worsening of asthma was considered missing and was replaced with the worst prior observation of that test day.

Type 1 error was controlled only within the primary endpoint, with T5, T2.5, and T1.25 tested in order against placebo, then with T5 tested in order against T1.25 and T2.5, then with T2.5 tested against T1.25.

3.2.2.3 Study 443

Endpoints for study 443 were analyzed using analysis of covariance (ANCOVA), with treatment as a fixed effect and with baseline value as a continuous covariate. Statistical tests were conducted at the two-sided 0.05 level of significance.

Secondary PFT endpoints were summarized using descriptive statistics.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

There were no obvious differences between treatments for baseline characteristics in the submitted studies (Appendix A; Table 21, Table 22, Table 23, and Table 24). There was minimal missing data, and patterns of patient disposition did not contradict efficacy of T5, T2.5, or T1.25 (Table 5, Table 6, Table 7, and Table 8).

Table 5. Disposition, Study 445

	Pbo		**T2.5**		**T5**	
	N	**(%)**	**N**	**(%)**	**N**	**(%)**
Randomized	132		136		135	
Treated	131	(100.0%)	135	(100.0%)	135	(100.0%)
Not prematurely discontinued treatment	122	(93.1%)	130	(96.3%)	130	(96.3%)
Prematurely discontinued treatment	9	(6.9%)	5	(3.7%)	5	(3.7%)
Adverse events (AE)	0		0		0	
Lack of efficacy	0		0		0	
Non-compliant with protocol	1	(0.8%)	0		0	
Lost to follow-up	0		2	(1.5%)	0	
Consent withdrawn (not due to AE)	4	(3.1%)	3	(2.2%)	2	(1.5%)
Other	4	(3.1%)	0		3	(2.2%)

Source: CSR Table 10.1:1

Table 6. Disposition, Study 446

	Pbo		T2.5		T5	
	N	(%)	N	(%)	N	(%)
Randomized	134		137		130	
Treated	134	(100.0%)	136	(100.0%)	130	(100.0%)
Not prematurely discontinued treatment	130	(97.0%)	136	(100.0%)	126	(96.9%)
Prematurely discontinued treatment	4	(3.0%)	0		4	(3.1%)
Adverse events (AEs)	2	(1.5%)	0		2	(1.5%)
Worsening of asthma	0		0		2	(1.5%)
Worsening of other pre-existing disease	0		0		0	
Other AE	2	(1.5%)	0		0	
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	(0.7%)	0		1	(0.8%)
Other	1	(0.7%)	0		1	(0.8%)

Source: CSR Table 10.1:1

Table 7. Patient Disposition, Study 425

	Pbo	T1.25	T2.5	T5
	N (%)	N (%)	N (%)	N (%)
Entered/randomized	77	76	74	76
Treated	76 (100.0%)	75 (100.0%)	74 (100.0%)	76 (100.0%)
Not prematurely discontinued treatment	76 (100.0%)	75 (100.0%)	74 (100.0%)	75 (98.7%)
Prematurely discontinued treatment	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
Reason for discontinuation				
Consent withdrawn not due to AE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)

Source: CSR Table 10.1:1

Table 8. Patient Disposition, Study 433

	Pbo N (%)	T2.5 N (%)	T5 N (%)
Randomized	34	36	32
Treated	34 (100.0%)	36 (100.0%)	31 (100.0%)
Not prematurely discontinued treatment	34 (100.0%)	36 (100.0%)	31 (100.0%)

Source: CSR Table 10.1:1

3.2.4 Results and Conclusions

3.2.4.2 Primary Endpoint: Peak $FEV_{1,0\text{-}3hr}$ in Six to Eleven Year Olds

In studies 445 and 425, conducted in six to eleven year olds with moderate asthma, T5 and T2.5 were superior to Pbo for the primary endpoint, peak $FEV_{1,0\text{-}3\ hr}$ (Table 10, Table 11). Study 425 also included T1.25, which was superior to placebo (Table 11). No dose-related numerical trends or statistically significant difference between doses were apparent (Table 10, Table 12).

In trial 446, which enrolled six to eleven year olds with severe asthma, there was no significant difference between T2.5 and Pbo for the primary and secondary endpoints. The 5 mcg/day arm, however was significantly superior to placebo. Several possible explanations for the lack of T2.5 efficacy in study 446 were evaluated: (i) Time of evaluation; in study 446, endpoints were measured at week 12, while study 445 endpoints were measured at week 24, suggesting that study 446 was not conducted for an adequate time to achieve treatment effects. However, in crossover study 425, significant treatment effects were achieved by week 4; (ii) Type 2 error; it is possible that a real treatment effect of T2.5 was missed due to random chance in study 446, however this possibility cannot be reliably evaluated; (iii) Greater use of long acting beta-2 agonists (LABA) in study 446; while more patients used LABA in study 446 than in the other two studies, within study 446 comparisons between patients on or off LABA showed no significant differences, with a p-value of .14 for LABA by treatment interaction. The point estimate for the difference between T2.5 and Pbo at week 12 was equal to 0.061 liters (95% CI: -0.079, 0.202) for patients not administered concurrent LABA and was equal to 0.022 liters (95% CI: -0.049, 0.094) for patients administered LABA; and (iv) Asthma severity; that trial 446 alone enrolled patients with severe persistent asthma rather than patients with moderate persistent asthma suggests that, to achieve an effect, patients with severe persistent asthma may require larger doses than patients with moderate persistent asthma. The medical team will consider the results of study 446 and prior studies of Spiriva Respimat when deciding on the final approved pediatric dose or indication.

In summary, three trials conducted in six to eleven year olds with moderate (studies 425 and 445) or severe (study 446) asthma showed statistically significant treatment effects of tiotropium for the primary endpoint, Δ peak $FEV_{1,0\text{-}3\ hr}$. However, in trial 446, conducted in patients with severe rather than moderate asthma, the dosage required to achieve a significant effect exceeded the currently approved dosage.

Table 10. Δ Peak $FEV_{1,0\text{-}3hr}$ in Six to Eleven Year Olds, Studies 445 and 446

Study	Week	Δ Peak $FEV_{1,0\text{-}3hr}$ (N)			Mean Difference (p-value) (95% CI)		
		T5	T2.5	Pbo	T5-Pbo	T2.5-Pbo	T5-T2.5
445	24	0.389	0.395	0.225	0.164	0.170	-0.006
		(134)	(131)	(126)	(<.0001)	(<.0001)	(.9)
					(0.103, 0.225)	(0.108, 0.231)	(-0.066, 0.055)
	48	0.477	0.474	0.351	0.127	0.124	0.003
		(130)	(130)	(124)	(<.0001)	(<.0001)	(.9)
					(0.065, 0.188)	(0.062, 0.185)	(-0.058, 0.064)
446	12	0.391	0.287	0.252	0.139	0.035	0.104
		(128)	(135)	(130)	(<.0001)	(.3)	(.001)
					(0.075, 0.203)	(-0.028, 0.099)	(0.040, 0.167)

source: reviewer programs s445 mmrm 2016 10 21.sas , S446 mmrm.sas, CSR Study 45 Table 15.2.1.1.: 1, CSR Study 46 Table 11.4 1 1 1: 1

Table 11. Δ Peak $FEV_{1,0\text{-}3hr}$ in Six to Eleven Year Olds, Study 425, Comparisons to Placebo

Week	Δ Peak $FEV_{1,0\text{-}3hr}$ (N)				Mean Difference (p-value) (95% CI)		
	T5	T2.5	T1.25	Pbo	T5-Pbo	T2.5-Pbo	T1.25-Pbo
4	0.272	0.29	0.261	0.185	0.087	0.104	0.075
	(100)	(100)	(100)	(100)	(<.001)	(<.0001)	(.001)
					(0.042, 0.132)	(0.059, 0.149)	(0.03, 0.12)

source: reviewer program S425 mmrm.sas, CSR Table 11.4.1.1.1: 1

Table 12. Δ Peak $FEV_{1,0\text{-}3hr}$ in Six to Eleven Year Olds, Study 425, Between Dose Comparisons

Week	Δ Peak $FEV_{1,0\text{-}3hr}$ (N)				Mean Difference (p-value) (95% CI)		
	T5	T2.5	T1.25	Pbo	T5-T2.5	T5-T1.25	T2.5-T1.25
4	0.272	0.290	0.261	0.185	-0.017	0.012	0.029
	(100)	(100)	(100)	(100)	(.5)	(.6)	(.2)
					(-0.063, 0.028)	(-0.034, 0.057)	(-0.016, 0.074)

source: reviewer program S425 mmrm.sas, CSR Table 11.4.1.1.1: 1

Table 13. Δ Peak $FEV_{1,0\text{-}3hr}$ in Six to Eleven Year Olds, Study 446. Impact of LABA on Treatment Effect

LABA	Δ Peak $FEV_{1,0\text{-}3hr}$ (N)			Difference (p-value) (95% CI)		
	T5	T2.5	Pbo	T5-Pbo	T2.5-Pbo	T5-T2.5
No	0.422 (29)	0.252 (33)	0.190 (23)	0.232 (<.001) (0.102, 0.363)	0.061 (.4) (-0.079, 0.202)	0.171 (.02) (0.027, 0.315)
Yes	0.380 (99)	0.294 (97)	0.272 (112)	0.108 (.004) (0.034, 0.182)	0.022 (.5) (-0.049, 0.094)	0.086 (.02) (0.015, 0.157)

source: reviewer program concom 2017 01 12.sas

3.2.4.3 *Secondary Endpoint: Δ Trough FEV_1 in Six to Eleven Year Olds*

Echoing the results for the primary endpoint, in studies 445 and 425, conducted in six to eleven year olds with moderate asthma, T2.5 and T5 were superior to Pbo (Table 14, Table 15). Study 425 also included T1.25, which was also superior to placebo (Table 15). No statistically significant difference between doses were observed (Table 14, Table 16).

At weeks 8 and 12, T5 was superior to T2.5 for study 446 but not for study 445 (Table 14), again suggesting that, in pediatric patients with severe asthma, the optimal dose may be T5 rather than T2.5.

Table 14. Δ Trough FEV_1 in Six to Eleven Year Olds, Studies 445 and 446

Study	Week	Δ Trough FEV_1 (N)			Difference (p-value) (95% CI)		
		T5	T2.5	Pbo	T5-Pbo	T2.5-Pbo	T5-T2.5
445	12	0.239 (134)	0.221 (134)	0.152 (129)	0.087 (.01) (0.017, 0.156)	0.069 (.051) (0, 0.139)	0.017 (.6) (-0.051, 0.086)
	24	0.274 (134)	0.272 (131)	0.156 (126)	0.118 (.001) (0.048, 0.188)	0.116 (.001) (0.046, 0.186)	0.002 (.96) (-0.067, 0.071)
	48	0.365 (130)	0.337 (130)	0.266 (124)	0.099 (.006) (0.029, 0.17)	0.071 (.048) (0.001, 0.142)	0.028 (.4) (-0.041, 0.097)
446	4	0.190 (130)	0.144 (135)	0.088 (129)	0.102 (.003) (0.034, 0.169)	0.056 (.1) (-0.011, 0.122)	0.046 (.2) (-0.021, 0.113)
	8	0.218 (129)	0.15 (132)	0.126 (130)	0.092 (.008) (0.024, 0.159)	0.024 (.5) (-0.043, 0.091)	0.068 (.046) (0.001, 0.135)
	12	0.223 (128)	0.154 (135)	0.136 (130)	0.087 (.01) (0.019, 0.154)	0.018 (.6) (-0.048, 0.085)	0.069 (.044) (0.002, 0.135)

source: reviewer programs s445 mmrm 2016 10 21.sas , S446 mmrm.sas , CSR Study 45 Tables 15.2.2.1.: 1 , CSR Study 46 Tables 15.2.2.1.: 1

Table 15. Δ Trough FEV_1 in Six to Eleven Year Olds, Study 25, Comparisons to Placebo

Week	Δ Trough FEV_1 (N)				Difference (p-value) (95% CI)		
	T5	T2.5	T1.25	Pbo	T5-Pbo	T2.5-Pbo	T1.25-Pbo
4	0.183 (100)	0.190 (100)	0.160 (100)	0.085 (100)	0.098 (<.0001) (0.051, 0.146)	0.105 (<.0001) (0.057, 0.153)	0.075 (.002) (0.027, 0.123)

source: reviewer program S425 mmrm.sas, CSR Table 15.2.1.2.1: 1

Table 16. Δ Trough FEV_1 in Six to Eleven Year Olds, Study 425, Between Dose Comparisons

Week	Δ Trough FEV_1 (N)				Difference (p-value) (95% CI)		
	T5	T2.5	T1.25	Pbo	T5-T2.5	T5-T1.25	T2.5-T1.25
4	0.183 (100)	0.190 (100)	0.160 (100)	0.085 (100)	-0.006 (.8) (-0.055, 0.042)	0.024 (.3) (-0.024, 0.072)	0.03 (.2) (-0.018, 0.078)

source: reviewer program S425 mmrm.sas, CSR Table 15.2.1.2.1: 1

3.2.4.4 Exploratory Endpoints: Patient Reported Outcomes

No significant differences or consistently favorable trends between tiotropium and placebo were seen for ACQ-IA (Table 17), PAQLQ(S) (Table 18), or change from baseline asthma symptom score (Table 19). It is unclear whether the lack of differences between treatment and placebo indicates a failure of improvements in pulmonary function to result in improvements in how patients feel, or whether, instead, the sensitivity and/or reliability of the patient reported outcomes was inadequate to capture improvements in how patients feel.

Table 17. ACQ-IA in Six to Eleven Year Olds, Studies 445 and 446

Study	Wk	ACQ-IA (N)			Difference (p-value) (95% CI)		
		T5	T2.5	Pbo	T5-Pbo	T2.5-Pbo	T5-T2.5
445	12	1.033 (134)	0.97 (134)	1.068 (130)	-0.035 (.6) (-0.176, 0.105)	-0.099 (.2) (-0.239, 0.042)	0.063 (.4) (-0.076, 0.203)
	24	0.835 (134)	0.897 (131)	1.017 (126)	-0.182 (.01) (-0.323, -0.04)	-0.12 (.1) (-0.262, 0.022)	-0.062 (.4) (-0.202, 0.078)
	48	0.723 (130)	0.752 (130)	0.817 (124)	-0.093 (.2) (-0.236, 0.049)	-0.065 (.4) (-0.208, 0.078)	-0.029 (.7) (-0.17, 0.112)
446	4	1.200 (130)	1.162 (136)	1.321 (129)	-0.121 (.12) (-0.275, 0.032)	-0.158 (.042) (-0.311, -0.006)	0.037 (.6) (-0.116, 0.19)
	8	1.084 (129)	1.061 (134)	1.189 (130)	-0.105 (.2) (-0.258, 0.049)	-0.128 (.1) (-0.281, 0.025)	0.023 (.8) (-0.13, 0.177)
	12	0.948 (126)	1.046 (136)	1.026 (130)	-0.079 (.3) (-0.233, 0.076)	0.02 (.8) (-0.133, 0.173)	-0.099 (.2) (-0.252, 0.055)

Source: reviewer program s445 mmrm 2016 12 02.sas, s446 mmrm 2016 12 02.sas , study 445 CSR Table 15.2.3.3.1.1: 1, study 446 CSR table 15.2.3.3.1.1: 1

Table 18. PAQLQ(S) in Six to Eleven Year Olds, Studies 425 and 444

Study	Week	PAQLQ(S) (N)			Difference (p-value) (95% CI)		
		T5	T2.5	Pbo	T5-Pbo	T2.5-Pbo	T5-T2.5
445	24	6.093 (134)	6.142 (131)	5.966 (126)	0.127 (.07) (-0.013, 0.267)	0.176 (.01) (0.035, 0.316)	-0.049 (.5) (-0.187, 0.09)
	48	6.327 (130)	6.288 (130)	6.309 (124)	0.017 (.8) (-0.124, 0.158)	-0.021 (.8) (-0.163, 0.12)	0.039 (.6) (-0.1, 0.178)
425	4	6.200 (100)	6.138 (100)	6.109 (100)	0.091 (.11) (-0.021, 0.204)	0.029 (.6) (-0.085, 0.142)	0.063 (.3) (-0.051, 0.177)

Source: reviewer program s445 mmrm 2016 12 02.sas, s425 mmrm 2016 12 02.sas, study 445 CSR Table 15.2.3.3.2.1: 1, study 425 CSR table 15.2.1.3.3: 1

Table 19. Δ Asthma Symptom Score in Six to Eleven Year Olds, Studies 445 and 446

Study	Week	Δ Asthma Symptom Score (N)			Difference (p-value) (95% CI)		
		T5	T2.5	Pbo	T5-Pbo	T2.5-Pbo	T5-T2.5
445	12	-0.15 (133)	-0.13 (130)	-0.10 (125)	-0.059 (.2) (-0.15, 0.032)	-0.037 (.4) (-0.128, 0.054)	-0.022 (.6) (-0.112, 0.068)
	24	-0.22 (130)	-0.14 (130)	-0.14 (122)	-0.082 (.08) (-0.173, 0.01)	0.001 (.99) (-0.091, 0.092)	-0.082 (.07) (-0.173, 0.008)
	48	-0.22 (125)	-0.23 (122)	-0.18 (119)	-0.043 (.4) (-0.136, 0.049)	-0.053 (.3) (-0.145, 0.04)	0.009 (.8) (-0.082, 0.101)
446	4	-0.08 (130)	-0.11 (136)	-0.09 (130)	0.008 (.9) (-0.089, 0.106)	-0.023 (.6) (-0.12, 0.073)	0.032 (.5) (-0.065, 0.128)
	8	-0.19 (128)	-0.17 (135)	-0.12 (130)	-0.07 (.2) (-0.168, 0.027)	-0.059 (.2) (-0.155, 0.038)	-0.012 (.8) (-0.109, 0.085)
	12	-0.22 (126)	-0.21 (136)	-0.21 (128)	-0.015 (.8) (-0.112, 0.083)	-0.006 (.9) (-0.103, 0.091)	-0.009 (.9) (-0.106, 0.088)

Source: reviewer program s445 mmrm 2016 12 02.sas, s446 mmrm 2016 12 02.sas , study 445 CSR Table 15.2 3 2.4: 2, study 446 CSR table 15.2.3.2.4: 2

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup (sex, USA vs non-USA, race, ethnicity) specific differences in treatment effects for the primary endpoint, Δ peak $FEV_{1,0\text{-}3hr}$, were evaluated by adding subgroup and subgroup by treatment interaction terms to the analysis model. As evidenced by the treatment by subgroup interactions, for the six to eleven year olds, there was no evidence of an impact of sex on treatment effect (study 25 p=.56, study 45 p=.16, study 46 p=.92), of race on treatment effect (study 25 all patients white, study 445 p=.85, study 446 p=.92), or of ethnicity on treatment effect (study 25 no Hispanics, study 45 p=.83, study 46 p=.66).

The treatment by country (USA, not USA) interaction term could not be evaluated in study 25 (no patients in USA) and was not significant in study 45 (p=.92). However, in study 46, the treatment by country interaction term was statistically significant in study 46 (p=.007). Further evaluation (Table 20) suggests that the difference between T5 and T2.5 is higher within the United States than outside the United States. As noted in section 3.2.4.2 above regarding the significant difference between T5 and T2.5 in study 446, the medical team will consider this result taking into account prior studies of Spiriva Respimat when deciding on the final approved pediatric dose or indication.

Table 20. Δ Peak $FEV_{1,0\text{-}3hr}$ in Six to Eleven Year Olds, Study 446. Impact of Country

USA	**Δ Peak $FEV_{1,0\text{-}3hr}$ (N)**			**Difference (p-value) (95% CI)**		
	T5	**T2.5**	**Pbo**	**T5-Pbo**	**T2.5-Pbo**	**T5-T2.5**
No	0.363 (123)	0.278 (130)	0.233 (126)	0.129 (<.000) (0.065, 0.194)	0.045 (.2) (-0.019, 0.108)	0.085 (.01) (0.021, 0.149)
Yes	0.83 (5)	0.289 (5)	0.488 (4)	0.342 (.051) (-0.001, 0.686)	-0.199 (.3) (-0.542, 0.144)	0.541 (.001) (0.217, 0.865)

Source: reviewer program s446 mmrm subgr 2017 01 19.sas

5 SUMMARY AND CONCLUSIONS

5.1 Statistical issues

There are no outstanding statistical issues from this submission.

5.2 Collective Evidence

Compared to placebo, the collective evidence demonstrates a clear effect of tiotropium on change from baseline peak FEV_1 within 3 hours of treatment and on change from baseline trough FEV_1. There is also evidence, from a single study that, in patients with severe persistent asthma, T5 is more effective than T2.5. Despite improvements on these pulmonary function tests, none of the doses impacted patient/caretaker reported outcomes such as ACQ-IA, PAQLQ(S), and change from baseline asthma symptom score.

5.3 Conclusions and Recommendations

The present submission provides results from three randomized, double blind, parallel arm trials, studies 443, 445, and 446, and one randomized, incomplete crossover trial, study 425, to evaluate the efficacy of Spiriva Respimat (tiotropium) for the treatment of asthma in pediatric patients.

Studies 425, 445, and 446, were conducted in patients 6 to 11 years of age. Studies 425 and 445 enrolled patients with moderate persistent asthma, and study 446 enrolled patients with severe persistent asthma, All three studies included T5), T2.5, and Pbo. In addition, study 425 included T1.25.

In trials 425 and 445, conducted in patients with moderate persistent asthma, T2.5, the approved dose for asthma in adolescent and adult patients, was superior to placebo for the primary endpoint, change from baseline peak $FEV_{1,0\text{-}3hr}$, and for the key secondary endpoint, change from baseline trough FEV_1.

However, in trial 446, which enrolled patients with severe rather than moderate asthma, there was no significant difference between T2.5 and Pbo for the primary and secondary endpoints. T5, however, was significantly superior to placebo. Several possible explanations for the lack of T2.5 efficacy in study 446 were evaluated: (i) Time of evaluation; in study 446, endpoints were measured at week 12, while study 445 endpoints were measured at week 24, suggesting that study 446 was not conducted for an adequate time to achieve treatment effects. However, in crossover study 425, significant treatment effects were achieved by week 4; (ii) Type 2 error; it is possible that a real treatment effect of T2.5 was missed due to random chance in study 446, however this possibility cannot be reliably evaluated; (iii) Greater use of long acting beta-2 agonists (LABA) in study 446; while more patients used LABA in study 446 than in the other two studies, within study 446 comparisons between patients on or off LABA showed no significant differences, with a p-value of .14 for LABA by treatment interaction. The point estimate for the difference between T2.5 and Pbo at week 12 was equal to 0.061 liters (95% CI: -0.079, 0.202) for patients not administered concurrent LABA and was equal to 0.022 liters (95% CI: -0.049, 0.094) for patients administered LABA; and (iv) Asthma severity; that trial 446 alone enrolled patients with severe persistent asthma rather than patients with moderate persistent asthma suggests that, to achieve an effect, patients with severe persistent asthma may require larger doses than patients with moderate persistent asthma. The medical team will consider the results of study 446 and prior studies of Spiriva Respimat when deciding on the final approved pediatric dose or indication.

Despite superiority for the primary and key secondary pulmonary function test endpoints, none of the three trials in six to eleven year-olds showed significant effects on patient-reported or caretaker-reported outcomes such as interviewer administered asthma control questionnaire, standardized pediatric asthma quality of life questionnaire, or change from baseline asthma symptom score.

(b) (4)

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In conclusion, for 6 to 11 year olds who have moderate persistent asthma, this submission provides substantial evidence of effectiveness for T2.5, the dosage approved for asthma in adults and adolescents. For 6 to 11 year olds who have severe persistent asthma, it seems possible that a higher dose, T5, may be required to achieve a treatment effect. (b) (4)

5.4 Labeling Recommendations

The indication proposed by the sponsor is for "the long-term, once-daily, maintenance treatment of asthma in patients (b) (4) of age and older." (b) (4) patients 6 years of age and older.

The approved dosage of Spiriva Respimat for asthma is 2.5 mcg/day. Given potential lack of efficacy for this dosage in study 446, the clinical team should consider whether 2.5 mcg/day is adequate for pediatric patients with severe persistent asthma. In addition, even if this product approved for such patients, the label should clearly convey the lack of demonstrated treatment effects in that population.

6 Appendix: Baseline Demographic Characteristics

Table 21. Patient Demographics, Study 445

	Pbo N (%)	**T2.5 N (%)**	**T5 N (%)**
Number of patients	131 (100.0%)	135 (100.0%)	135 (100.0%)
Sex			
Male	85 (64.9%)	97 (71.9%)	82 (60.7%)
Female	46 (35.1%)	38 (28.1%)	53 (39.3%)
Race			
American Indian/Alaska Native	16 (12.2%)	15 (11.1%)	14 (10.4%)
Asian	2 (1.5%)	4 (3.0%)	4 (3.0%)
Black/African American	1 (0.8%)	3 (2.2%)	3 (2.2%)
Hawaiian/Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)
White	112 (85.5%)	113 (83.7%)	114 (84.4%)
Hispanic/Latino	18 (13.7%)	18 (13.3%)	19 (14.1%)
Age Mean (SD)	9.0 (1.6)	9.0 (1.6)	8.9 (1.7)
Age class			
<6 years	0 (0.0%)	0 (0.0%)	0 (0.0%)
6-8 years	49 (37.4%)	53 (39.3%)	59 (43.7%)
9-11 years	82 (62.6%)	82 (60.7%)	76 (56.3%)
>11 years	0 (0.0%)	0 (0.0%)	0 (0.0%)

source: CSR Table 11 2 1:1

Table 22. Patient Demographics, Study 446

	Pbo N (%)	**T2.5 N (%)**	**T5 N (%)**
Number of patients	134 (100.0%)	136 (100.0%)	130 (100.0%)
Sex			
Male	93 (69.4%)	96 (70.6%)	90 (69.2%)
Female	41 (30.6%)	40 (29.4%)	40 (30.8%)
Race			
American Indian/Alaska Native	11 (8.2%)	11 (8.1%)	13 (10%)
Asian	1 (0.7%)	0 (0.0%)	1 (0.8%)
Black/African American	1 (0.7%)	3 (2.2%)	1 (0.8%)
Hawaiian/Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)
White	121 (90.3%)	122 (89.7%)	115 (88.5%)
Hispanic/Latino	28 (20.9%)	23 (16.9%)	21 (16.2%)
Age Mean (SD)	9.1 (1.6)	8.8 (1.7)	9.2 (1.6)
Age class			
<6 years	0 (0.0%)	0 (0.0%)	0 (0.0%)
6-8 years	49 (37.4%)	53 (39.3%)	59 (43.7%)
9-11 years	82 (62.6%)	82 (60.7%)	76 (56.3%)
>11 years	0 (0.0%)	0 (0.0%)	0 (0.0%)

source: CSR Table 11 2 1:1

Table 23. Patient Demographics, Study 425

	N (%)
Number of patients	101 (100.0%)
Sex	
Male	69 (68.3%)
Female	32 (31.7%)
Race	
White	101 (100%)
Hispanic/Latino	0 (0%)
Age Mean (SD)	8.8 (1.7)
Age class	
<6 years	0 (0.0%)
6-8 years	37 (36.6%)
9-11 years	64 (63.4%)
>11 years	0 (0.0%)

source: CSR Table 11 2 1:1

Table 24. Patient Demographics, Study 443

	Pbo		T2.5		T5	
	N	(%)	N	(%)	N	(%)
Number of patients	34	(100.0%)	36	(100.0%)	31	(100.0%)
Sex						
Male	21	(61.8%)	19	(52.8%)	21	(67.7%)
Female	13	(38.2%)	17	(47.2%)	10	(32.3%)
Race						
White	24	(70.6%)	28	(77.8%)	25	(80.6%)
Asian	7	(20.6%)	5	(13.9%)	5	(16.1%)
Black/African American	3	(8.8%)	3	(8.3%)	1	(3.2%)
Hispanic/Latino	0	(0%)	06	(0%)	0	(0%)
Age Mean (SD)	3.2	(1.4)	3.1	(1.5)	3.1	(1.3)

source: CSR Table 11 2 1:1

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/s/

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