Common Drug Review
Clinical Review Report

July 2015

Drug	tiotropium bromide monohydrate (Spiriva Respimat) for oral inhalation
Indication	For the long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, and for the reduction of exacerbations.
Listing request	In a manner similar to Spiriva HandiHaler
Manufacturer	Boehringer Ingelheim Canada Ltd.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

AE	adverse event
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CDR	CADTH Common Drug Review
CRF	Case Report Form
CTS	Canadian Thoracic Society
CV	cardiovascular
DAS	death analysis set
DB	double-blind
ECSC	European Community for Coal and Steel
FAS	full-analysis set
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
HR	hazard ratio
ICS	inhaled corticosteroids
ITT	intention-to-treat
LABA	long-acting beta-2 agonist
LAMA	long-acting muscarinic antagonist
MACE	major adverse cardiovascular events
MCID	minimal clinically important difference
MDI	metered dose inhaler
MI	myocardial infarction
MTC	mixed treatment comparison
OR	odds ratio
PP	per-protocol
QoL	quality of life
RCT	randomized controlled trial
SABA	short-acting beta-2 agonist
SAE	serious adverse event
SAMA	short-acting muscarinic receptor antagonist
SD	standard deviation
SGRQ	St. George's Respiratory Questionnaire
SSS	spirometry sub-study
TDI	Transition Dyspnea Index
Tio R 5	Spiriva Respimat 5 mcg once daily
Tio R 10	Spiriva Respimat 10 mcg once daily
Tio H 18	Spiriva HandiHaler 18 mcg once daily
TS	treated set
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Chronic obstructive pulmonary disease (COPD) is a respiratory disorder characterized by progressive, partially reversible airway obstruction and lung hyperinflation, systemic manifestations, and increasing frequency and severity of exacerbations. Pathological changes in the lung vary among individuals, but usually involve a combination of airway inflammation (chronic bronchitis) and parenchymal destruction (emphysema). Bronchodilator therapy with short- or long-acting inhaled beta-2 agonists (SABAs, LABAs) or short- or long-acting muscarinic antagonists (SAMAs, LAMAs) is a mainstay of COPD therapy. Tiotropium bromide is an inhaled LAMA that has been approved in Canada since 2002 as the Spiriva HandiHaler (Tio H 18), which is administered as an 18 mcg once-daily dose via a dry powder inhalation. Spiriva Respimat (Tio R 5) is a new multi-dose, propellant-free, aerosol delivery device for tiotropium, administered as a 5 mcg once-daily dose (two actuations of 2.5 mcg) through an aqueous inhalation solution. Spiriva Respimat is indicated for long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema, and for the reduction of exacerbations. The recommended dose is two inhalations of 2.5 mcg tiotropium (5 mcg) once daily through the Respimat device.

The objective of the review was to evaluate the beneficial and harmful effects of Tio R 5 in adult patients with moderate-to-severe COPD.

Results and Interpretation

Included Studies

Eight prospective, DB randomized controlled trials (RCTs) met the selection criteria for inclusion in the review: studies 205.249 (N = 131),[1] 205.250 (N = 76),[2] 205.251 (N = 361),[3] 205.252 (N = 358), 205.254 (N = 983),[4] 205.255 (N = 1,007),[5] 205.372, (N = 3,991), and 205.452 (TIOSPIR) (N = 17,183). All trials included patients who were at least 40 years of age, had a diagnosis of moderate-to-severe COPD (according to the European Community for Coal and Steel [ECSC] criteria), and a history of smoking (at least 10 pack-years). The primary efficacy outcome in studies 205.249, 205.250, 205.251, and 205.252 was trough forced expiratory volume in one second (FEV_1) response. In studies 205.254 and 205.255, there were four co-primary end points (trough FEV_1 response, St. George's Respiratory Questionnaire [SGRQ], Transition Dyspnea Index [TDI], and COPD exacerbations). There were two co-primary end points in each of Study 205.372 (trough FEV_1 response and time to first COPD exacerbation) and Study 205.452 (time to death from any cause and time to first COPD exacerbation). All efficacy end points were analyzed using the full-analysis set (FAS) population or FAS subsets, depending upon the outcome.

A key limitation among the included non-inferiority trials is the uncertainty regarding the clinical significance of the results and the methodology used to establish the non-inferiority margin of 0.05 L for the trough FEV_1 response. Other important limitations are baseline characteristics (e.g., underrepresentation of female patients, predominance of Caucasian patients) and study design factors (e.g., exclusion of patients who had previously received tiotropium from the majority of trials and use of a less-than-optimal dose of ipratropium), which limit the generalizability of the study findings to Canadian COPD patients.

Efficacy

Key efficacy outcomes identified in the review protocol included mortality, health care resource utilization, COPD exacerbations, quality of life (QoL), pulmonary function testing, COPD symptoms, and exercise tolerance. Both the Spiriva HandiHaler and Spiriva Respimat devices have similar Health Canada–approved indications for the long-term (i.e., once-daily maintenance treatment of airflow obstruction in patients with COPD), with the exception that Spiriva Respimat is also indicated for the reduction of exacerbations.[6,7] A key consideration is how the two products compare, as the efficacy and safety of Spiriva HandiHaler has been established and it has been available on the Canadian market for more than a decade. Therefore, the focus will be on the three trials that directly compared Tio R 5 with Tio H 18 on the efficacy outcomes of mortality and COPD exacerbations (TIOSPIR) and trough FEV_1 response (studies 205.249 and 205.250, and TIOSPIR).

There were few deaths in the included trials of shorter duration (205.249 and 205.250: 28 weeks; and 205.251 and 205.252: 12 weeks). The number of deaths increased in the trials of longer duration (205.254 and 205.255: one year), and there was a suggestion of an imbalance in the number of deaths associated with Tio R 5. This led to the undertaking of Study 205.372 (N = 3,991; one year's duration) that compared Tio R 5 with placebo; 52 deaths (2.7%) were reported in the Tio R 5 group and 38 deaths (1.9%) were reported in the placebo group after one year. Although there were more deaths in the Tio R 5 group, an analysis of fatal events revealed a non-statistically significant rate ratio of all fatal events of 1.38 (95% confidence interval [CI], 0.91 to 2.10). Similarly, the rate ratios of fatal events due to cardiac disorders (2.27 [95% CI, 0.70 to 7.37]), lower respiratory system disorders (0.57 [95% CI, 0.25 to 1.28]), or other respiratory system disorders (2.52 [95% CI, 0.49 to 13.01]) were not statistically significant.

To further investigate a potential mortality risk associated with Tio R 5, the large-scale TIOSPIR study (N = 17,183; approximately three years' duration) was initiated. TIOSPIR was a multi-centre, parallel-group, DB RCT that compared the efficacy and safety of Tio R 2.5 (not reported as this is not a Health Canada–approved dose), Tio R 5, and Tio H 18 in patients with COPD. The purpose of this trial was to provide prospective data from a trial of adequate size and duration to establish that Tio R 5, compared with Tio H 18, has (a) similar effects on mortality, and (b) similar or superior effects on reductions of COPD exacerbations. The study was designed to test for non-inferiority of the co-primary end point of time to death (all-cause mortality), and superiority for the second co-primary end point of time to first COPD exacerbation. The non-inferiority margin for time to death was based on the upper bound of the 95% CI for the hazard ratio (HR) being below 1.25. At study completion, there were 423 deaths (7.4%) in the Tio R 5 group and 439 deaths (7.7%) in the Tio H 18 group over the three years. The corresponding HR was 0.957 (95% CI, 0.837 to 1.094), which met the pre-specified, non-inferiority margin for the HR of all-cause death, thus supporting that the mortality risk was similar between Tio R 5 and Tio H 18. As the UPLIFT trial[8,9] had shown a similar mortality rate in patients on Tio H 18 compared with placebo, Health Canada concluded that the results from the TIOSPIR study provided sufficient evidence to alleviate the concerns about an increased mortality risk associated with Spiriva Respimat.[10]

The analysis of COPD exacerbations in TIOSPIR revealed that similar proportions of patients in the Tio R 5 group (47.9%) and the Tio H 18 group (48.9%) had a COPD exacerbation, corresponding with a non-statistically significant HR of 0.978 (95% CI, 0.928 to 1.032). The proportions of patients who had moderate-to-severe COPD exacerbations were also similar between treatment groups: Tio R 5 (47.2%) and Tio H 18 (48.0%) (HR = 0.983 [95% CI, 0.932 to 1.037]), as were the proportions of patients with hospitalizations due to COPD exacerbations: Tio R 5 (14.5%) and Tio H 18 (14.3%) (HR = 1.024 [95% CI, 0.929 to 1.128]).

Studies 205.254, 205.255, and 205.372, in which Tio R 5 was compared with placebo over one-year treatment periods, also support that Tio R 5 is associated with statistically significant reductions in COPD exacerbations, moderate-to-severe COPD exacerbations, time to first COPD exacerbation, and hospitalizations due to COPD exacerbations when compared with placebo.

All three trials (205.249, 205.250 and TIOSPIR) that directly compared Tio R 5 and Tio H 18 included the outcome of trough FEV_1 response. Trough FEV_1 response at the end of each four-week treatment period was the primary outcome in studies 205.249 and 205.250, which were identical crossover, multi-centre, DB RCTs that compared four 4-week treatment periods of Tio R 5, Tio R 10 (not reported as this is not a Health Canada–approved dose), Tio H 18, and placebo in patients with moderate-to-severe COPD. Treatment differences were statistically significant for the tests of superiority of each of Tio R 5 and Tio H 18 compared with placebo. Non-inferiority of Tio R 5 with Tio H 18 was also demonstrated in both trials, based on the pre-specified, non-inferiority margin of 0.05 L (i.e., non-inferiority was concluded if at a (one-sided) $P < 0.025$, the lower bound of the 95% CI for the absolute difference in trough FEV_1 was above –0.50 L). The lower CI bound was 0.013 ($P < 0.001$) for non-inferiority in Study 205.249 and the lower CI bound was –0.039 ($P = 0.006$) for non-inferiority in Study 205.250. The magnitude of the treatment differences in trough FEV_1 response compared with placebo exceeded the minimal clinically important difference (MCID) of 0.100 L for Tio R 5 in both studies (i.e., 0.116 L in Study 205.249 and 0.126 L in Study 205.250) and for Tio H 18 in Study 205.250 (0.125 L), but not for Tio H 18 in Study 205.249 (0.070 L). The per-protocol (PP) non-inferiority analyses based on the trough FEV_1 response confirmed the results in the FAS population.

A subset of patients from TIOSPIR participated in a spirometry sub-study (SSS) in which the key secondary end point of trough FEV_1 response was also evaluated for non-inferiority of Tio R 5 and Tio H 18. In contrast to the other non-inferiority comparisons for trough FEV_1 response in the applicable trials included in the review, TIOSPIR was the only trial in which it was explicitly stated that the choice of the non-inferiority margin was based on the lower bound of the 95% CI for the absolute difference in trough FEV_1 lying above –0.05 L. The comparison of trough FEV_1 response through 120 weeks in the sub-study demonstrated that the adjusted mean treatment difference between Tio R 5 (n = 461) and Tio H 18 (n = 445) was –0.010 L (95% CI, –0.038 to 0.018), thus meeting the pre-specified margin for non-inferiority.

Trough FEV_1 response was the primary outcome in studies 205.251 and 205.252, which compared Tio R 5, ipratropium 36 mcg four times daily (Iprat 36), and placebo. Treatment differences in trough FEV_1 response at the end of 12 weeks were statistically significant in favour of Tio R 5 compared with placebo, and the MCID was exceeded in both studies. In contrast, treatment differences between Iprat 36 and placebo did not reach statistical significance and did not exceed the MCID for trough FEV_1 response in either study. Non-inferiority of Tio R 5 with Iprat 36 was demonstrated in both trials, based on the pre-specified non-inferiority margin of 0.05 L (i.e., non-inferiority was concluded if at a (one-sided) $P < 0.025$, the lower bound of the 95% CI for the absolute difference in trough FEV_1 was above –0.50 L, the pre-specified non-inferiority margin). The lower CI bound was –0.024 ($P < 0.0041$) for non-inferiority in Study 205.251, and the lower CI bound was 0.024 ($P < 0.001$) for non-inferiority in Study 205.252. Tio R 5 also demonstrated superiority versus Iprat 36 (two-sided $P = 0.005$ for superiority) in Study 205.252, but not in Study 205.251 (two-sided $P = 0.1897$ for superiority). Overall, the reason for these observations (i.e., lack of superiority for Iprat 36 over placebo and superiority of Tio R 5 over Iprat 36 in only one study) is unclear, although it may have been due to the use of a less-than-optimal dose of ipratropium in these trials. According to the clinical expert involved in the review, in clinical practice an ipratropium dose of twice this magnitude (72 mcg, four times per day) has been used. If the Iprat 36 dose is not

reflective of current clinical practice, this may have implications for the generalizability of the results of the data from these trials to the Canadian COPD population

In studies 205.254, 205.255, and 205.372, which evaluated the superiority of Tio R 5 to placebo, the treatment differences in trough FEV_1 response after one year of treatment were statistically significant in favour of Tio R 5 when compared with placebo in all three trials. The magnitude of the treatment differences between Tio R 5 and placebo all exceeded the MCID of 0.100 L.

Outcomes that were evaluated in only some of the included trials are QoL and COPD symptoms. None of the trials included the outcomes of health care resource utilization (with the exception of hospitalization due to COPD exacerbations) or exercise tolerance. In studies 205.254, 205.255, and 205.372, Tio R 5 was associated with statistically significant improvements in SGRQ total scores and domain scores over one year of treatment. The differences in SGRQ total scores between Tio R 5 and placebo were –3.269 (95% CI, –5.224 to –1.315) in Study 205.254, –3.713 (95% CI, –5.778 to –1.647) in Study 205.255, and –2.9 (95% CI, –3.9 to –2.0) in Study 205.372, none of which met the MCID of a difference of ≥ 4 points for SGRQ total score.

In studies 205.251 and 205.252, statistically significant differences in COPD symptom scores at 12 weeks between Tio R 5 and placebo or between Tio R 5 and Iprat 36 were not observed for all symptoms, and results were inconsistent between the two trials. In contrast, in studies 205.254 and 205.255, statistically significant treatment differences at the end of one year of treatment were found for all comparisons of Tio R 5 versus placebo for all COPD symptom scores. In addition, statistically significant treatment differences in Mahler TDI focal scores between Tio R 5 and placebo (1.104 in Study 205.254 and 1.011 in Study 205.255) were also observed, and the differences exceeded the MCID (improvement of at least one unit from the Baseline Dyspnea Index [BDI]).

Across all trials, the use of rescue medication (salbutamol metered dose inhaler [MDI]) was similar between Tio R 5 and Tio H 18, and was less frequent than with placebo treatment. Patient compliance or adherence to study medication was high across all studies (i.e., compliance was > 95% with all devices [Respimat, HandiHaler, or MDI]). In Study 205.252, a patient satisfaction questionnaire was administered at US study sites only. Overall, there was a high degree of satisfaction with both the Respimat inhaler and the Iprat 36 MDI; however, the sample size was small (approximately 50 patients), so the results should be interpreted with caution.

In studies with co-primary end points (205.254, 205.255, 205.372, and TIOSPIR), results were consistent with regard to the statistical significance of the co-primary end points within the trials, thus providing confidence in the results. As detailed in Appendix 1: Patient Input Summary, outcomes important to patients with COPD are symptom relief, impact on activities of daily living, caregiver burden, and the challenges associated with compliance with and the correct use of inhalers or devices. Of these, the only outcome that was addressed in the included trials was COPD symptoms, although as discussed previously, the data are limited and the results were inconsistent among the identically designed trials.

Harms

Overall, the harms data support that Tio R 5 and Tio H 18 have comparable safety and tolerability profiles. In TIOSPIR, the proportions of patients with adverse events (AEs) (64.9% versus 65.5%), serious AEs (SAEs) (18.8% versus 18.6%), and withdrawals due to AEs (WDAEs) (8.2% versus 8.8%) were very similar between Tio R 5 and Tio H 18, respectively. The most frequently reported AE, which was also the most frequent SAE and reason for WDAEs, was COPD exacerbations. More patients in the Tio R 5 groups

of the trials experienced dry mouth. There did not appear to be any clear association of pneumonia AEs with any one treatment. In Study 205.252, 3.4% of patients in the Iprat 36 group and no patients in the Tio R 5 or placebo groups had an AE of atrial fibrillation, which was not reported with any other treatment. Overall, the frequency of cardiovascular (CV)-related AEs was low across the included trials. In Study 205.452, additional safety analyses were conducted related to CV-related AEs, which included analyses of the incidence of major adverse cardiovascular events (MACE), stroke, myocardial infarction (MI), and transient ischemic attacks (TIAs). In all analyses, no statistically significant differences were found between Tio R 5 and Tio H 18 for any of these outcomes.

Conclusions

Eight prospective, DB RCTs met the selection criteria for inclusion in the review, three of which directly compared Tio R 5 with Tio H 18 in patients with moderate-to-severe COPD. A key limitation is the uncertainty regarding the clinical significance of the results and the methodology used to establish the non-inferiority margin of 0.05 L for trough FEV_1 response in some of the trials. Other limitations are baseline characteristics and study design factors that limit the generalizability of the study findings to Canadian COPD patients. Based on the non-inferiority margin for trough FEV_1 response pre-specified by the manufacturer, Tio R 5 was shown to be non-inferior to Tio H 18. Tio R 5 was also shown to have similar effects on reducing COPD exacerbations when compared with Tio H 18. Results from other included trials support that Tio R 5 is superior to placebo in reducing COPD exacerbations, improving QoL (SGRQ total score), improving TDI focal scores, and improving various COPD symptoms. The harms data support that Tio R 5 and Tio H 18 had similar safety profiles, as the proportions of patients with AEs, SAEs, and WDAEs with each treatment were similar. The most frequently reported AE regardless of treatment, which was also the most frequent SAE and reason for WDAEs, was COPD exacerbations. Despite the suggestion of an increased mortality risk with Spiriva Respimat based on early trials and a mixed treatment comparison (MTC)[11] that compared Spiriva Respimat with Tio H 18, LABA, ICS/LABA combinations, and ICS alone, it was shown in the prospective large-scale TIOSPIR study that the proportions of deaths between Tio R 5 and Tio H 18 were similar over a three-year period.

TABLE 1A: SUMMARY OF RESULTS

Study No.	205.249			205.250			205.251			205.252		
Treatment Arm	**Tio R 5**	**Tio H 18**	**PL**	**Tio R 5**	**Tio H 18**	**PL**	**Tio R 5**	**Iprat 36**	**PL**	**Tio R 5**	**Iprat 36**	**PL**
Duration	**28 Weeks (4-Week Txt Periods)**						**12 Weeks**					
Mortality, n (%)												
Deaths	2 (1.5)			2 (2.6)			0 (0)	0 (0)	0 (0)	1 (1.1)	1 (1.1)	0 (0)
CV-related	2 (1.5)			0 (0)			0 (0)	0 (0)	0 (0)	1 (1.1)	0 (0)	0 (0)
COPD-related	0 (0)			2 (2.6)			0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	0 (0)			0 (0)			0 (0)	0 (0)	0 (0)	0 (0)	1 (1.1)	0 (0)
Spirometry: Trough FEV_1 (L)												
Baseline mean (SD)	1.011 (0.392)			1.121 (0.362)			1.146 (0.367)	1.248 (0.401)	1.244 (0.395)	0.995 (0.417)	0.957 (0.409)	1.130 (0.426)
Txt diff at EOT, mean (95% CI) or mean (SE)	**Tio R 5 vs. PL:** 0.116 (0.083 to 0.149) *P* < 0.001 (Superiority)[a] **Tio R 5 vs. Tio H 18:** 0.045 (0.013 to 0.078) *P* < 0.001 (Non-inferiority)[a, b, c] **Tio H 18 vs. PL:** 0.070 (0.037 to 0.104) *P* < 0.001 (Superiority)[a]			**Tio R 5 vs. PL:** 0.126 (0.086 to 0.166) *P* < 0.001 (Superiority)[a] **Tio R 5 vs. Tio H 18:** 0.001 (–0.039 to 0.041) *P* = 0.006 (Non-inferiority)[a, b, c] **Tio H 18 vs. PL:** 0.125 (0.085 to 0.165) *P* < 0.001 (Superiority)[a]			**Tio R 5 vs. PL:** 0.109 (0.036 to 0.181) *P* = 0.0034[d] (Superiority) **Tio R 5 vs. Iprat 36:** 0.049 (–0.024 to 0.122); *P* = 0.0041[b] (Non-inferiority); *P* = 0.1897[d] (Superiority) **Iprat 36 vs. PL:** 0.060 (SE = 0.037[e]) *P* = 0.1045[d] (Superiority)			**Tio R 5 vs. PL:** 0.124 (0.067 to 0.181) *P* < 0.0001[d] (Superiority) **Tio R 5 vs. Iprat 36:** 0.080 (0.024 to 0.136) *P* < 0.0001[b] (Non-inferiority); *P* = 0.0055 (Superiority) **Iprat 36 vs. PL:** 0.044 (SE = 0.029[e]) *P* = 0.1373[d] (Superiority)		
COPD Symptoms												
Baseline, mean[f] Wheezing SOB Coughing Tightness of chest	NR						0.8 1.6 1.1 0.6			0.8 1.6 1.0 0.5		
Txt diff at day 85, mean (SE); *P* value Wheezing SOB Coughing Tightness of chest	NR						**Tio R 5 vs. PL:** –0.1 (0.1); *P* = 0.4414 –0.1 (0.1); *P* = 0.3966 –0.1 (0.1); *P* = 0.4128 –0.3 (0.1); *P* = 0.0039			**Tio R 5 vs. PL:** –0.3 (0.1); *P* = 0.0156 0.0 (0.1); *P* = 0.6631 –0.1 (0.1); *P* = 0.2222 –0.1 (0.1); *P* = 0.1713		

Study No.	205.249			205.250			205.251			205.252		
Treatment Arm	Tio R 5	Tio H 18	PL	Tio R 5	Tio H 18	PL	Tio R 5	Iprat 36	PL	Tio R 5	Iprat 36	PL
Duration	28 Weeks (4-Week Txt Periods)									12 Weeks		
Withdrawals, n (%)	38 (29.0)			4 (5.3)			8 (9.1)	17 (19.1)	7 (7.7)	8 (8.7)	14 (15.7)	15 (16.7)
AEs, n (%)	32 (28.6)	31 (27.7)	36 (33.3)	41 (54.7)	33 (44.0)	55 (72.4)	42 (47.7)	49 (55.1)	45 (49.5)	53 (57.6)	57 (64.0)	62 (68.9)
SAEs, n (%)	5 (4.5)	4 (3.6)	5 (4.6)	2 (2.7)	1 (1.3)	2 (2.6)	2 (2.3)	8 (9.0)	4 (4.4)	2 (2.2)	9 (10.1)	1 (1.1)
WDAEs, n (%)	3 (2.7)	4 (3.6)	12 (11.1)	1 (1.3)	0 (0)	2 (2.6)	6 (6.8)	11 (12.4)	5 (5.5)	7 (7.6)	9 (10.1)	11 (12.2)

AE = adverse event; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; Diff = differences; EOT = end of treatment; FEV_1 = forced expiratory volume in one second; HRQoL = health-related quality of life; Iprat 36 = ipratropium 36 mcg, four times daily dose; NR = not reported; PL = placebo; Pts = patients; SAE = serious adverse event; SD = standard deviation; SE = standard error; SGRQ = St. George's Respiratory Questionnaire; SOB = shortness of breath; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; Tio R 5 = Spiriva Respimat; Txt=treatment
5 mcg daily dose; Txt = treatment; WDAE = withdrawal due to adverse event.

[a] *P* values are one-sided.

[b] Non-inferiority was concluded if at a (one-sided) $P < 0.025$, the lower bound of the 95% CI for the absolute difference in trough FEV_1 was above –0.50 L, the pre-specified non-inferiority margin.

[c] No test for superiority with Tio R 5 versus Tio H 18 was performed.

[d] *P* values are two-sided.

[e] Only SE (no 95% CIs) was reported in the Clinical Study Report for the comparison between Iprat 36 and PL.

[f] For studies 205.251 and 205.252, only the common baseline mean was reported in the respective Clinical Study Reports.

Note: COPD symptoms were not measured in studies 205.249 and 205.250, and COPD exacerbations and HRQoL were not measured in any of studies 205.249, 205.250, 205.251, or 205.252.

Source: Clinical Study Report (CSR) 205.249,[1] CSR 205.250,[2] CSR 205.251,[3] and CSR 205.252.[12]

TABLE 1B: SUMMARY OF RESULTS (CONTINUED)

Study No.	205.254		205.255		205.372		205.452 (TIOSPIR)	
Treatment Arm	Tio R 5	PL	Tio R 5	PL	Tio R 5	PL	Tio R 5	Tio H 18
Duration	48 Weeks						3 Years	
Mortality, n (%)								
All-cause deaths	7 (2.1)	5 (1.6)	5 (1.5)	0 (0)	52 (2.7)	38 (1.9)	423 (7.4)	439 (7.7)
CV-related	1 (0.3)	0 (0)	1 (3.3)	0 (0)	9 (0.5)	4 (0.2)	27 (0.5)	17 (0.3)
COPD-related[a]	1 (0.3)	0 (0)	1 (3.3)	0 (0)	0 (0)	0 (0)	123 (2.2)	130 (2.3)
Other	5 (1.5)	5 (1.6)	3 (0.9)	0 (0)	43 (2.2)	34 (1.7)	273 (4.8)	292 (5.1)
All-cause death rate (95% CI)					RR: 1.38 (0.91 to 2.10)		HR: 0.957 (0.837 to 1.094)[b]	
COPD Exacerbations[c]								
Pts with ≥ 1 exacerbation, n (%)	Tio R 5: 249 (37.2) PL: 288 (44.1)				685 (35.3)	842 (43.1)	2,733 (47.9)	2,782 (48.9)
Rate ratio (95% CI)	OR=0.75 (0.60 to 0.93)				HR = 0.693 (0.625 to 0.769)		HR = 0.978 (0.928 to 1.032)	
Pts with ≥ 1 moderate-to-severe exacerbation, n (%)	NR				538 (27.7)	666 (34.1)	2,694 (47.2)	2,732 (48.0)
Rate ratio (95% CI)	NR				HR = 0.699 (0.622 to 0.786)		HR = 0.983 (0.932 to 1.037)	
Pts with ≥ 1 hospitalization, n (%)	Tio R 5: 39 (5.8) PL: 44 (6.7)				161 (8.3)	198 (10.1)	826 (14.5)	811 (14.3)
Rate ratio (95% CI)	NR				HR = 0.728 (0.589 to 0.901)		HR = 1.024 (0.929 to 1.128)	
HRQoL: SGRQ Total Scores								
Baseline mean[d]	44.930		44.719		43.5 (18.2)	44.8 (18.3)	NR	NR
Txt diff at day 337, mean (95% CI)	–3.269 (–5.224 to –1.315)		–3.713 (–5.778 to –1.647)		–2.9 (–3.9 to –2.0)		NR	NR
Spirometry: Trough FEV_1 (L)								
Baseline mean (SD or SE)[e]	1.049 (0.370)	1.085 (0.373)	1.087 (0.420)	1.049 (0.40)	1.111 (0.009)	1.106 (0.009)	Results from SSS: Tio R 5 (n = 461): 1.285 (0.012) Tio H 18 (n = 445): 1.295 (0.012) Txt diff: –0.010 (–0.038 to 0.018)[f]	
Txt diff at day 337, mean (95% CI); *P* value	0.142 (0.104 to 0.181)		0.113 (0.078 to 0.147)		0.102 (0.085 to 0.118)			
COPD Symptoms								
Baseline mean[d]								
Wheezing	0.87		0.77		NR			
SOB	1.66		1.67					
Coughing	1.20		1.10					
Tightness of chest	0.80		0.68					

Study No.	205.254		205.255		205.372		205.452 (TIOSPIR)	
Treatment Arm	**Tio R 5**	**PL**	**Tio R 5**	**PL**	**Tio R 5**	**PL**	**Tio R 5**	**Tio H 18**
Duration	**48 Weeks**						**3 Years**	
Txt diff at day 337, mean (SE); *P* value								
Wheezing	–0.24 (0.05); *P* < 0.0001		–0.19 (0.05); *P* = 0.0003					
SOB	–0.16 (0.05); *P* = 0.0027		–0.19 (0.05); *P* = 0.0006					
Coughing	–0.16 (0.06); *P* = 0.0037		–0.10 (0.06); *P* = 0.0773					
Tightness of chest	–0.16 (0.05); *P* = 0.0014		–0.13 (0.05); *P* = 0.0107					
Txt diff at day 337, mean (SE); *P* value								
Wheezing	–0.24 (0.05); *P* < 0.0001		–0.19 (0.05); *P* = 0.0003					
SOB	–0.16 (0.05); *P* = 0.0027		–0.19 (0.05); *P* = 0.0006					
Coughing	–0.16 (0.06); *P* = 0.0037		–0.10 (0.06); *P* = 0.0773					
Tightness of chest	–0.16 (0.05); *P* = 0.0014		–0.13 (0.05); *P* = 0.0107					
Withdrawals, n (%)	55 (16.6)	91 (28.5)	60 (17.8)	114 (34.1)	318 (16.0)	373 (18.6)	1,306 (22.9)	1,287 (22.6)
AEs, n (%)	240 (72.3)	236 (74.0)	265 (78.4)	266 (79.6)	1,369 (70.1)	1,361 (69.3)	3,701 (64.9)	3,727 (65.5)
SAEs, n (%)	45 (13.6)	54 (16.9)	63 (18.6)	56 (16.8)	342 (17.5)	336 (17.1)	1,846 (32.4)	1,842 (32.4)
WDAEs, n (%)	31 (9.3)	47 (14.7)	36 (10.7)	74 (22.2)	136 (7.0)	149 (7.6)	468 (8.2)	498 (8.8)

AE = adverse event; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; Diff = difference; FEV_1 = forced expiratory volume in one second; HR = hazard ratio; HRQoL = health-related quality of life; NR = not reported; OR = odds ratio; PL = placebo; Pts = patients; RR = rate ratio; SAE = serious adverse event; SD = standard deviation; SE = standard error; SGRQ = St. George's Respiratory Questionnaire; SOB = shortness of breath; SSS = spirometry sub-study; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; Tio R 5 = Spiriva Respimat 5 mcg daily dose; Txt = treatment; WDAE = withdrawal due to adverse event.

[a] For Study 205.452, COPD-related deaths are all deaths reported in the system organ class of "Respiratory, Thoracic, and Mediastinal Disorders."

[b] Non-inferiority between Tio R 5 and Tio H 18 was concluded if the upper limit of 95% CI for the HR was below 1.25, the pre-specified non-inferiority margin.

[c] For studies 205.254 and 205.255, results for COPD exacerbations were only available from a pooled analysis of the trials.

[d] For studies 205.254 and 205.255, only the common unadjusted baseline mean was reported.

[e] For studies 205.254 and 205.255, the value in parentheses is SD, and for Study 205.372 the value in parentheses is SE.

[f] Non-inferiority between Tio R 5 and Tio H 18 was achieved if the lower bound of the 95% CI for the absolute difference in trough FEV_1 was above –0.50 L, the pre-specified non-inferiority margin.

Note: Severity of COPD exacerbations was not reported in either Study 205.254 or 205.255, and COPD symptoms were not measured in either Study 205.372 or 205.452.

Source: Clinical Study Report (CSR) 205.254,[4] CSR 205.255,[5] CSR 205.372,[13] CSR 205.452,[14] and Bateman et al., 2010.[15]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Chronic obstructive pulmonary disease (COPD) is a respiratory disorder characterized by progressive, partially reversible airway obstruction and lung hyperinflation, systemic manifestations, and increasing frequency and severity of exacerbations.[16,17] Pathological changes in the lung vary among individuals, but usually involve a combination of airway inflammation (chronic bronchitis) and parenchymal destruction (emphysema).[18] There is significant overlap of COPD subtypes, with many individuals presenting with features of both chronic bronchitis and emphysema, as well as asthma, which differs fundamentally from COPD.[17] COPD is largely caused by smoking and it is associated with multiple comorbid conditions (e.g., diabetes, ischemic heart disease, muscle wasting, bone loss, anemia, cancer, anxiety, and depression).[17]

COPD is a major public health problem and is a leading cause of morbidity and mortality worldwide, comprising an economic and social burden that is both substantial and increasing.[19] According to a 2009 Statistics Canada report, COPD affects 4% of the Canadian population ≥ 35 years of age.[20] Among COPD patients in Canada aged 35 to 79 years, 7% had stage II (moderate) or higher COPD.[21] Diagnosing and determining the severity of COPD typically requires the use of spirometry. The two indicators necessary for establishing a diagnosis of COPD are forced expiratory volume in one second (FEV_1), which is the amount of air that one can expel in one second, and forced vital capacity (FVC), which is the amount of air that one can expel upon full inspiration with no limit to the duration of expiration. A post-bronchodilator FEV_1/FVC ratio < 0.7 indicates airway obstruction. The Canadian Thoracic Society (CTS) classification of COPD severity is summarized in Table 2.

TABLE 2: CTS CLASSIFICATION OF COPD SEVERITY BY SYMPTOMS, DISABILITIES, AND IMPAIRMENT OF LUNG FUNCTION

COPD Stage	Spirometry (Post-bronchodilator)	Symptoms
I: Mild	$FEV_1 \geq 80\%$ predicted, $FEV_1/FVC < 0.7$	Shortness of breath from COPD when hurrying on the level or walking up a slight hill.
II: Moderate	$50\% \leq FEV_1 < 80\%$ predicted, $FEV_1/FVC < 0.7$	Shortness of breath from COPD causing the patient to stop after walking approximately 100 m (or after a few minutes on the level).
III: Severe	$30\% \leq FEV_1 < 50\%$ predicted, $FEV_1/FVC < 0.7$	Shortness of breath from COPD resulting in the patient being too breathless to leave the house, breathless when dressing or undressing, or the presence of chronic respiratory failure or clinical signs of right heart failure.
IV: Very severe	$FEV_1 < 30\%$ predicted, $FEV_1/FVC < 0.7$	NA

COPD = chronic obstructive pulmonary disease; CTS = Canadian Thoracic Society; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; NA = not available.Source: O'Donnell et al., 2007.[16]

COPD is associated with an increased risk of mortality, and was ranked as the fourth leading cause of death in Canada in 2004.[16] By 2020, COPD is projected to become the third leading cause of death worldwide.[19] COPD is associated with high rates of admissions and readmissions to hospital (i.e., of all COPD patients hospitalized in 2006 to 2007, 18% of COPD patients were readmitted once and 14% were admitted twice).[22] Hospital admissions for COPD exacerbations averaged a 10-day length of stay at a cost of $10,000 per stay. The total cost of COPD hospitalizations in Canada is estimated at $1.5 billion per year.[23]

1.2 Standards of Therapy

The goals of COPD management are to prevent disease progression, reduce the frequency and severity of exacerbations, alleviate symptoms, improve exercise tolerance and daily activity, treat exacerbations and complications, improve health status, and reduce mortality.[16] Management decisions are guided by disease severity (i.e., symptoms/disability and spirometry) and the frequency of acute exacerbations.

Smoking cessation is the single most effective intervention to reduce the risk of developing COPD and the only intervention shown to slow the rate of lung function decline.[17] Regular exercise with cardiorespiratory conditioning can improve functional status and the sensation of dyspnea in COPD patients, more so than use of medications alone.

Bronchodilators form the mainstay of pharmacotherapy for COPD,[17] and include short-acting beta-2 agonists (SABAs) such as salbutamol and short-acting muscarinic antagonists (SAMAs) such as ipratropium. Long-acting beta-2 agonists (LABAs) such as salmeterol, formoterol, and indacaterol, or long-acting muscarinic antagonists (LAMAs) such as tiotropium, aclidinium, and glycopyrronium, as well as combinations of fixed-dose LABAs and inhaled corticosteroids (ICS) (i.e., ICS/LABA) such as fluticasone/salmeterol (Advair) or budesonide/formoterol (Symbicort), are the most commonly used treatments for COPD in Canada. Muscarinic antagonists and beta-2 agonists are often used in combination for maximal improvement in dyspnea and function. ICS may not be useful for mild disease; however, they may have more of a role in the management of patients with a history of exacerbations and moderate-to-severe COPD, or in those with persistent symptoms, when combined with a LABA.[24-26] There may also be a subpopulation of COPD patients that have concomitant asthma or airway eosinophilia, where ICS use may be beneficial.[27-29] Phosphodiesterase inhibitors (theophylline, and more recently, roflumilast) are adjunctive therapies for COPD management that may be more effective in those with demonstrable neutrophilic airway inflammation. Inhaled medications are most commonly delivered as pressurized metered dose inhalers (MDI) and dry powder inhalers.

Pulmonary rehabilitation is recommended for moderate-to-very severe COPD, while oxygen therapy is used in very severe COPD patients with persistent hypoxemia.

Acute exacerbations of COPD are managed with optimized bronchodilator therapy, oral or parenteral corticosteroids, and antibiotics.[17]

1.3 Drug

Tiotropium bromide monohydrate is a LAMA with a similar affinity for all five human muscarinic receptors, M_1 to M_5.[6] It is a quaternary ammonium molecule with long duration of action attributed to its slow dissociation kinetics from the M_3 receptor subtype, which is sufficient to provide 24 hours of bronchoprotection following administration by once-daily inhalation.[6] Tiotropium has been approved in Canada since 2002 as the Spiriva HandiHaler (Tio H 18), which provides 18 mcg tiotropium per capsule administered once daily using the HandiHaler device. Spiriva Respimat (Tio R 5) is a new multi-dose, propellant-free, aqueous, soft mist aerosol delivery device that provides 2.5 mcg tiotropium per actuation.[6] It is indicated for long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema, and for the reduction of exacerbations.[6] The recommended dose is two oral inhalations of 2.5 mcg (5 mcg) tiotropium administered as an aerosol once daily using the Respimat device.

Indication under review
For the long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, and for the reduction of exacerbations.
Listing criteria requested by sponsor
In a manner similar to Spiriva HandiHaler

TABLE 3: KEY CHARACTERISTICS OF TIOTROPIUM, ACLIDINIUM, GLYCOPYRRONIUM, AND UMECLIDINIUM

Drug	Tiotropium Bromide	Aclidinium Bromide	Glycopyrronium Bromide	Umeclidinium Bromide
Mechanism of Action	LAMA with high affinity for M_3 receptor subtype.	LAMA with similar potency for all (M_1 to M_5) receptor subtypes, but kinetically has a preference for M_3.	LAMA with high affinity for M_1, M_2, and M_3 receptor subtypes.	LAMA with activity across multiple receptor subtypes, but slow reversibility at M_3.
Indication[a]	**Respimat**: Long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema, and for the reduction of exacerbations. **HandiHaler**: Long-term, once-daily maintenance treatment of bronchospasm associated with COPD, including bronchitis and emphysema.	Long-term maintenance bronchodilator treatment in patients with COPD, including bronchitis and emphysema.	Long-term, once-daily maintenance bronchodilator treatment in adult patients with COPD, including chronic bronchitis and emphysema.	Long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema.
Route of Admin-istration	**Respimat**: Oral inhalation of a soft mist (2.5 mcg per actuation). **HandiHaler**: Oral inhalation of dry powder (18 mcg per capsule).	Oral inhalation of dry powder (400 mcg) twice daily using the Genuair device.	Oral inhalation of dry powder (50 mcg) using the Breezhaler device.	Oral inhalation of dry powder (62.5 mcg umeclidinium and 25 mcg vilanterol) using the Ellipta device.
Recom-mended Dose	**Respimat**: 2 × 2.5 mcg once daily. **HandiHaler**: 1 × 18 mcg once daily.	400 mcg twice daily, once in the morning and once in the evening.	50 mcg once-daily inhalation.	62.5 mcg umeclidinium/25 mcg vilanterol once-daily inhalation.
Serious Side Effects/ Safety Issues	Anticholinergic effects (i.e., use with caution in patients with narrow-angle glaucoma, prostatic hyperplasia, or bladder-neck obstruction). Use only in patients with moderate-to-severe renal impairment if expected benefit outweighs potential risk.	Anticholinergic effects (i.e., use with caution in patients with narrow-angle glaucoma or urinary retention).	Anticholinergic effects (i.e., use with caution in patients with narrow-angle glaucoma or urinary retention). Use only in patients with severe renal impairment if expected benefit outweighs potential risk.	Risk of asthma-related death associated with LABAs (i.e., it is only indicated for COPD and safety and efficacy have not been established in patients with asthma). Contraindicated in patients with severe hypersensitivity to milk proteins. Similar warnings for anticholinergic effects as with other LAMAs.
Other/ Supplied	Spiriva Respimat multi-dose Soft Mist Inhaler. Spiriva HandiHaler dry powder inhaler.	Tudorza Genuair multi-dose dry powder inhaler.	Seebri Breezhaler single-dose dry powder inhaler.	Anoro Ellipta fixed-dose combination dry powder LAMA and LABA (vilanterol) inhaler.

COPD = chronic obstructive pulmonary disease; LABA = long-acting beta-2 agonist; LAMA = long-acting muscarinic antagonist.
[a] Health Canada indication.
Source: Product Monographs: Spiriva Respimat,[6] Spiriva HandiHaler,[7] Tudorza Genuair,[30] Seebri Breezhaler,[31] and Anoro Ellipta.[32]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of tiotropium bromide monohydrate 2.5 mcg per actuation administered through the Respimat Soft Mist Inhaler for the long-term maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema, and for the reduction of exacerbations.

2.2 Methods

Studies selected for inclusion in the systematic review included the pivotal studies provided in the manufacturer's submission to the CADTH Common Drug Review (CDR), as well as those meeting the selection criteria presented in Table 4.

TABLE 4: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult patients (≥ 18 years) with COPD including chronic bronchitis and/or emphysema. **Subgroups:** Age, sex, BMI, COPD severity, chronic bronchitis, emphysema, smoking status, concomitant CV disease.
Intervention	Tiotropium bromide 2.5 mcg per actuation administered as two inhalations once daily through the Respimat Soft Mist Inhaler.
Comparators	The following comparators used alone or in combination (as appropriate): • LAMA (e.g., aclidinium, glycopyrronium, umeclidinium, tiotropium [through the HandiHaler]) • SAMA (e.g., ipratropium) • SABA (e.g., salbutamol) • LABA (e.g., salmeterol, formoterol, indacaterol) • ICS (in combination only; e.g., ICS/LABA) • PDE4 inhibitors (e.g., roflumilast) • Theophylline
Outcomes	**Key efficacy outcomes:** • mortality (i.e., all-cause, CV-related, COPD-related) • health care resource utilization (e.g., hospitalization, ER visits) • COPD exacerbations • QoL with a validated measure (e.g., SGRQ) • pulmonary function tests (e.g., spirometric measures: FEV_1, IC) • symptoms (i.e., day and night, including dyspnea) • exercise tolerance **Other efficacy outcomes:** • rescue medication use • patient adherence or satisfaction • days of missed work or school **Harms outcomes:** AEs, SAEs, WDAEs, AEs of special interest (e.g., CV, pneumonia, anticholinergic AEs)
Study Design	Published and unpublished phase 3 RCTs

AE = adverse events; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; DB = double-blind; ER = emergency room; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; IC = inspiratory capacity; ICS = inhaled corticosteroids; LABA = long-acting beta-2 agonist; LAMA = long-acting muscarinic antagonist; PDE4 = phosphodiesterase type 4; QoL = quality of life; RCT = randomized controlled trial; SABA = short-acting beta-2 agonist; SAE = serious adverse event; SAMA = short-acting muscarinic antagonist; SGRQ = St. George's Respiratory Questionnaire; WDAE = withdrawal due to adverse event.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946 to present) with in-process records & daily updates via Ovid; Embase (1974 to present) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Spiriva-tiotropium (drug name) and Respimat (formulation).

Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on February 9, 2015. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) in June 2015. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trials. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Included studies are presented in Table 5 and excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings From the Literature

A total of eight studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 5 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

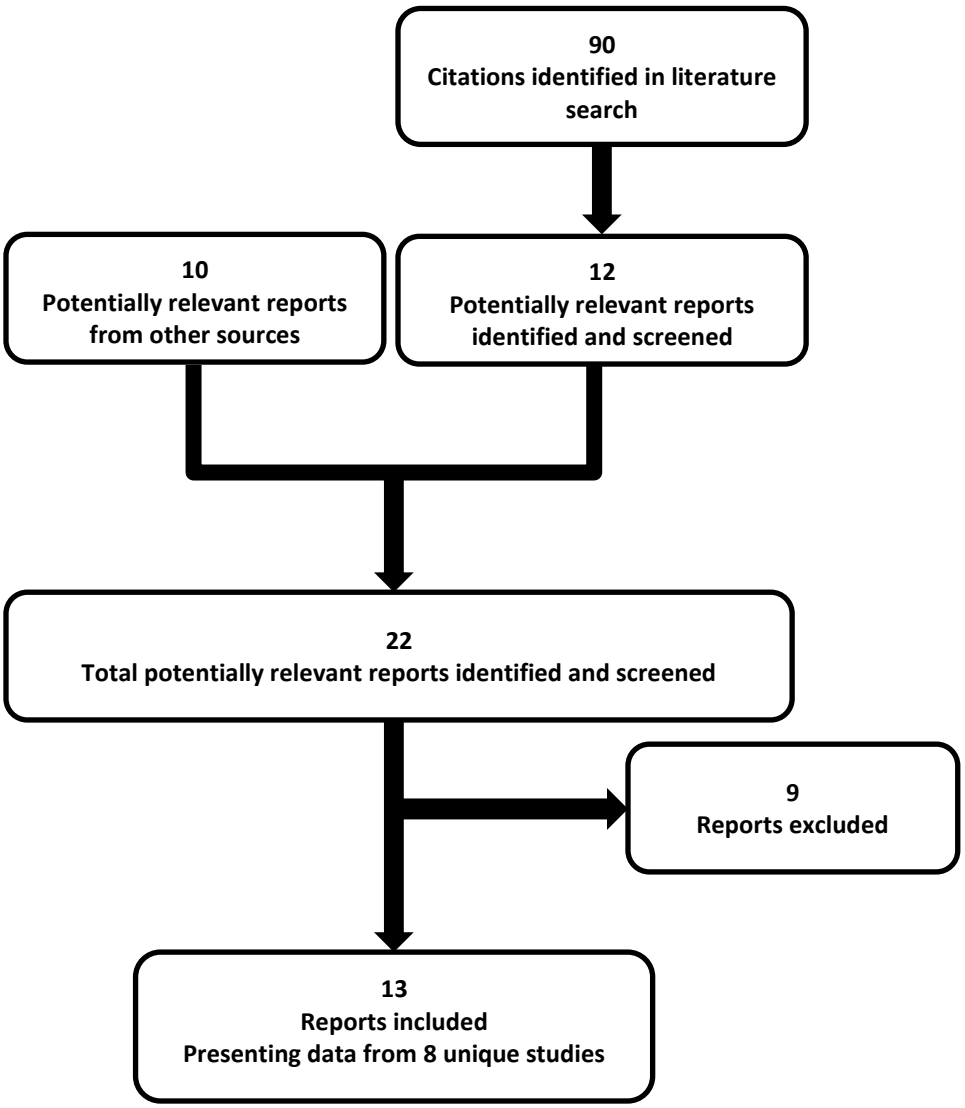

TABLE 5A: DETAILS OF INCLUDED STUDIES

	Study No.	205.249	205.250	205.251	205.252	205.254	205.255
DESIGNS & POPULATIONS	**Study Design**	Phase 3 or 2/3, MC, DB, DD, CX × 4 weeks RCT		Phase 3, MC, DB, DD, PG × 12 weeks RCT		Phase 3, MC, DB, PG × 1 year RCT	
	Locations	Canada, US	Netherlands Belgium	Europe, South Africa	Canada, US	Europe, Canada, US, Australia	
	Randomized (N)	131	76	361	358	983	1,007
	Inclusion Criteria	Adults ≥ 40 years with COPD (FEV_1 ≤ 60% predicted & FEV_1/FVC ≤ 70% by ECCS criteria), current or ex-smokers (> 10 pack-years)					
	Exclusion Criteria	Recent history of MI, cardiac arrhythmia, cancer, asthma, or significant disease other than COPD					
DRUGS	**Intervention**	Tio R 5 mcg (2 × 2.5 mcg inhalations) or 10 mcg (2 × 5 mcg inhalations) once daily[a]					
	Comparator(s)	Tio H 18 mcg or PL once daily by inhalation		Iprat 36 mcg four times daily or PL by inhalation		PL by inhalation	
DURATION	**Phase**						
	Run-in	2 weeks					
	DB	28 weeks (4 × 4-week periods + 3 × 4-week washouts)		12 weeks		48 weeks	
	Follow-up	None		3 weeks		3 weeks	
OUTCOMES	**Primary End Point**	Trough FEV_1 response				4 co-primary end points: trough FEV_1 response, SGRQ, TDI, COPD exacerbations	
	Other End Points	Other spirometry measures, use of rescue medication (salbutamol)		Other spirometry measures, use of rescue medication (salbutamol), COPD symptoms (i.e., wheezing, SOB, coughing, tightness of chest)			
NOTES	**Publications**	Van Noord et al., 2009[33]		Voshaar et al., 2008[34]		Bateman et al., 2010,[15] Hodder et. al., 2011[35]	

COPD = chronic obstructive pulmonary disease; CX = crossover; DB = double-blind; DD = double-dummy; ECCS = European Community for Coal and Steel; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; Iprat 36 = ipratropium 36 mcg, four times daily dose; MC = multi-centre; MI = myocardial infarction; PG = parallel-group; PL = placebo; RCT = randomized controlled trial; SGRQ = St. Georges Respiratory Questionnaire; SOB = shortness of breath; TDI = Transition Dyspnea Index; Tio H = Spiriva HandiHaler; Tio R = Spiriva Respimat.

[a] Data for the Tio R 10 mcg once-daily treatment groups are not included in this report as this is not a Health Canada–approved dose.

Note: Two additional reports were included (Manufacturer Submission;[36] Health Canada Reviewer's Report[10]).

Source: Clinical Study Report (CSR) 205.249,[1] CSR 205.250,[2] CSR 205.251,[3] CSR 205.252,[12] CSR 205.254,[4] and CSR 205.255.[5]

TABLE 5B: DETAILS OF INCLUDED STUDIES (CONTINUED)

	Study No.	205.372	205.452 (TIOSPIR)
Designs and Populations	**Study Design**	Phase 3b, MC, DB, PG × 1 year RCT	Phase 3b, MC, DB, DD, PG × 1 year RCT
	Locations	Europe, US, South Africa	Europe, Canada, US, China, South Africa, Australia
	Randomized (N)	3,991	17,183
	Inclusion Criteria	Adults ≥ 40 years with COPD (FEV_1 ≤ 60% predicted and FEV_1/FVC ≤ 70% by ECCS criteria), current or ex-smoker	Adults ≥ 40 years with COPD (FEV_1 ≤ 70% predicted and FEV_1/FVC ≤ 70% by ECCS criteria), current smoker or ex-smoker

	Study No.	205.372	205.452 (TIOSPIR)
	Exclusion Criteria	Recent MI, cardiac arrhythmia, asthma, or significant disease other than COPD	
Drugs	**Intervention**	Tio R 5 mcg once daily by inhalation	Tio R 2.5 mcg or 5 mcg once daily by inhalation[a]
	Comparator (s)	PL by inhalation	Tio H 18 mcg by inhalation
Duration	**Phase**		
	Run-in	7 days	NA
	DB	48 weeks	Event-driven (until 1,266 fatal events)
	Follow-up	4 weeks	30 days
Outcomes	**Primary End Point**	Co-primary: Trough FEV_1 response and time to first COPD exacerbation	Co-primary: Time to death from any cause and time to first COPD exacerbation
	Other End Points	Other spirometry measures, measures of COPD exacerbations, hospitalizations due to COPD exacerbations, and SGRQ	Other measures of COPD exacerbations and hospitalizations due to COPD exacerbations
Notes	**Publications**	Bateman et al., 2010[37]	Wise et al., 2013[38,39]

COPD = chronic obstructive pulmonary disease; DB = double-blind; DD = double-dummy; ECCS = European Community for Coal and Steel; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; MC = multi-centre; MI = myocardial infarction; NA = not applicable; PG = parallel-group; PL = placebo; RCT = randomized controlled trial; SGRQ = St. George's Respiratory Questionnaire; Tio H = Spiriva HandiHaler; Tio R = Spiriva Respimat.

[a] Data for the Tio R 2.5 mcg once-daily treatment group are not reported in this report as this is not a Health Canada–approved dose.

Note: Two additional reports were included (Manufacturer Submission[36] and Health Canada Reviewer's Report.[10]

Source: Clinical Study Reports 205.372[13] and 205.452.[14]

3.2 Included Studies

3.2.1 Description of Studies

A total of eight prospective randomized controlled trials (RCTs) met the selection criteria for inclusion in the systematic review: Studies 205.249 (N = 131),[1] 205.250 (N = 76),[2] 205.251 (N = 361),[3] and 205.252 (N = 358), 205.254 (N = 983),[4] 205.255 (N = 1,007),[5] 205.372, (N = 3,991), and 205.452 (TIOSPIR) (N = 17,183). In addition to investigating tiotropium 5 mcg (Tio R 5) once daily (two actuations of 2.5 mcg delivered by the Respimat inhaler), which is the Health Canada–approved dose for Spiriva Respimat, studies 205.249, 205.250, 205.251, and 205.252 also included a tiotropium 10 mcg (Tio R 10) once-daily group (two actuations of 5 mcg). Study 205.452 (TIOSPIR) also included a tiotropium 2.5 mcg once-daily group (Tio R 2.5). Data for the tiotropium 10 mcg and 2.5 mcg once-daily treatment groups from these trials are not included in this review as these are not approved doses for Spiriva Respimat in Canada.

Studies 205.249 and 205.250 were identical, 28-week, randomized, multi-centre, DB, double-dummy, placebo-controlled, crossover, non-inferiority and superiority, phase 3 and 2/3 trials, respectively. The trials compared four 4-week treatment periods of two doses of Tio R (5 mcg and 10 mcg) with tiotropium inhalation powder capsule (18 mcg) delivered by the HandiHaler device (Tio H 18) and double-dummy placebo in patients with COPD. The objective was to demonstrate the superiority of tiotropium (through the Respimat or HandiHaler) compared with placebo (based on the change from baseline in trough FEV_1 [trough FEV_1 response]), and then non-inferiority (based on trough FEV_1 response) of Tio R 5 and Tio R 10 versus Tio H 18. Following screening and a two-week run-in period, eligible patients were randomized to four 4-week treatment periods, each separated by a four-week washout period. Allocation to one of the four (out of 24) possible treatment sequences, forming a

William Square, was done at random. Randomization was performed in blocks of four patients to achieve balanced randomization. The allocated treatment sequence was determined according to randomization codes provided by a medical data services company, using a commercial program.

Studies 205.251 and 205.252 were identical, 12-week, randomized, multi-centre, DB, double-dummy, placebo- and active-controlled, parallel-group, non-inferiority, and superiority trials. The objective of the trials was to compare the bronchodilator efficacy and safety of Tio R 5 and Tio R 10 once daily with double-dummy placebo, and with ipratropium bromide inhalation aerosol 36 mcg (two actuations of 18 mcg) delivered by MDI four times daily (Iprat 36) in patients with COPD. The primary efficacy comparison was to demonstrate the bronchodilator superiority of tiotropium through the Respimat inhaler to placebo, then its non-inferiority to ipratropium MDI, and finally its superiority to ipratropium MDI. Following an initial screening visit and a two-week run-in period, patients were randomized to one of four treatment groups: Tio R 5, Tio R 10, Iprat 36, and placebo. Patients were randomized using a randomization list that was generated using a validated system involving a pseudo-random number generator. Randomization was conducted in blocks of four with equal allocation of the four treatments within each block.

Studies 205.254 and 205.255 were identical, 48-week, randomized, multi-centre, DB, placebo-controlled, parallel-group, phase 3 efficacy and safety studies designed to compare Tio R 5 and Tio R 10 once daily with placebo in patients with COPD. The objectives were to compare bronchodilator efficacy and effects on health status, as well as on dyspnea and frequency of COPD exacerbations. Following an initial screening and a two-week run-in period, patients were randomized to either tiotropium administered through the Respimat device or placebo. The primary efficacy comparison was to demonstrate the bronchodilatory superiority of each of the tiotropium doses to placebo. Patients were randomized using a randomization list generated by a validated system (ClinPro/LBL, version 5.2), which used a pseudo-number generator. Randomization was conducted in blocks of six, with equal allocation of the three treatment groups within each block.

Study 205.372 was a 48-week, randomized, DB, placebo-controlled, parallel-group phase 3b study to assess the long-term safety and superior efficacy of Tio R 5 once daily compared with placebo in patients with COPD. The purpose of this trial was to provide a second confirmatory study with Tio R 5 on its ability to reduce COPD exacerbations and to evaluate the bronchodilatory response in patients who were permitted to use all prescribed respiratory medications other than inhaled anticholinergics. The principal difference between this study and previous studies (i.e., 205.254 and 205.255) is that patients were allowed to continue their usual maintenance COPD therapy while on treatment with the study drug. The only medications that were excluded during the treatment period were anticholinergic bronchodilators other than the study drug. Thus, the placebo-control group was intended to reflect "usual care" for COPD (other than inhaled anticholinergics) as opposed to no active treatment.

Study 205.372 was also intended to enrich the safety database of Tio R 5. The follow-up of prematurely discontinued patients was pre-planned such that patients who withdrew prematurely were followed up regarding COPD exacerbations and vital status until their predicted normal exit date (plus 30 days). All patients attended a screening visit at which they were trained in the use of the Respimat inhaler. Seven days later, patients meeting the entry criteria were randomly assigned 1:1 to 48 weeks' treatment with either Tio R 5 or placebo (two puffs), both inhaled through the Respimat inhaler. Treatment allocation was determined by a computer-generated randomization code. Randomization was stratified by study centre and within centres, and performed in blocks to ensure a balanced distribution of treatment groups.

Study 205.452 (TIOSPIR) was a large-scale (50 countries, 1,280 sites), multi-centre, randomized, active-controlled, DB, double-dummy, parallel-group phase 3b trial to compare the efficacy and safety of Tio 2.5 and Tio R 5 once daily compared with Tio H 18 once daily in patients with COPD. This was an event-driven trial with a recruitment phase of 11 months, which was to continue until approximately 1,266 fatal adverse events (AEs) were reported. The purpose of this trial was to establish that, compared with tiotropium administered through the HandiHaler, tiotropium administered through Respimat has (a) similar effects on mortality, and (b) similar or superior effects on COPD exacerbations. TIOSPIR was designed to test for non-inferiority on the co-primary end point of time to death (all-cause mortality), and superiority for the second co-primary end point of time to first COPD exacerbation. Following screening, patients were randomized 1:1 to DB treatment using an interactive voice response system (IVRS) or interactive Web response system (IWRS). In addition to the study drugs, all patients received placebo concurrent with the corresponding active treatment as per the double-dummy design. A SSS in a subset of 1,370 patients (i.e., approximately 460 per treatment group) was also undertaken in TIOSPIR, in which spirometry was conducted every 24 weeks. Patients who withdrew prematurely continued to be followed up for vital status information until the event-driven end of trial. The trial continued for approximately three years and the actual number of deaths was 1,302.

In all studies, patients received training on the use of the Respimat, HandiHaler, or MDI devices, and were instructed on how to use the devices at home. At clinic visits, study personnel observed the inhalation procedures and reinforced correct inhalation techniques. Patients were required to record the administration of each dose of study medication and any concomitant medications on patient diary cards.

The pooling of data from the studies with identical protocols (i.e., 205.249 and 205.250, 205.252 and 205.253, and 205.254 and 205.255) was pre-specified in the study protocols for various outcomes.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

Inclusion criteria were similar across all eight included trials as per Table 5. All trials included adult male and female patients who were at least 40 years of age and who were current or former cigarette smokers (i.e., smoking history ≥ 10 pack-years). Patients were required to have a diagnosis of relatively stable, moderate-to-severe COPD according to the European Community for Coal and Steel (ECCS) criteria (i.e., FEV_1 ≤ 60% of predicted normal and FEV_1/FVC ≤ 70%), except for TIOSPIR where the FEV_1 ≤ 70% of predicted normal was used to permit inclusion of a population with a wider range of COPD severity. Key exclusion criteria are listed in Table 5 and as noted, patients with unstable or clinically significant cardiovascular (CV) conditions were excluded from the trials. This included patients who had a recent history (≤ 6 months) of myocardial infarction (MI), unstable or life-threatening cardiac arrhythmia, or hospitalization for heart failure in the past year. Patients with significant diseases other than COPD were excluded, if in the opinion of the investigator, the patient could have been at risk due to participation in the study or if the disease could have influenced the results of the study or the patient's ability to participate in the study.

In all studies, with the exception of studies 205.372 and TIOSPIR, a specific exclusion criterion was that patients who were receiving or who had previously received trial-sourced or commercially available tiotropium were excluded. This was done to avoid a potential selection bias based on a patient's previous response to tiotropium. In Study 205.372, patients who had previously participated in trials of Spiriva HandiHaler or had received treatment with commercially available Spiriva HandiHaler were eligible for inclusion provided that adequate washout requirements were met. In TIOSPIR, patients who had

previously received tiotropium were eligible for inclusion, and it does not appear a washout period was required.

In studies 205.249, 205.250, 205.251, 205.252, 205.254, and 205.255, patients with any respiratory infection or COPD exacerbation in the six weeks prior to the screening visit or during the run-in period were still eligible for participation, but randomization was postponed for six weeks following recovery from the infection or exacerbation.

b) Baseline Characteristics

Patient populations across the included trials were similar. In general, most patients were aged approximately 64 to 65 years and more than 50% of all patients were male, ranging from approximately 57% to 83% in individual treatment groups (Table 6). Almost all included patients were Caucasian (> 90%) with the exception of studies 205.372 and TIOSPIR, in which roughly 68% and 81% of patients, respectively, were Caucasian. The majority of included patients were ex-smokers (i.e., approximately 53% to 70% in individual treatment groups) with a long history of smoking (i.e., mean of 35 to 60 pack-years). A third or more of all patients (approximately 30% to 47%), were current smokers. In Study 205.252, there may have been a baseline imbalance in the number of current smokers (i.e., 30.4% in the Tio R 5 group versus 37.1% in the Iprat 36 group and 37.8% in the placebo group). The mean duration of COPD ranged from 7.4 to 11.4 years across individual study groups. The majority of patients had moderate-to-severe COPD as per ECCS criteria, which is also consistent with the CTS classification of COPD severity.[16] Overall, the baseline demographic and disease characteristics appeared to be well balanced between treatment groups and across trials.

TABLE 6A: SUMMARY OF BASELINE CHARACTERISTICS

Characteristic	Study No. and Treatment							
	205.249	205.250	205.251			205.252		
	N = 131	N = 76	Tio R 5 N = 88	Iprat 36 N = 89	PL N = 91	Tio R 5 N = 92	Iprat 36 N = 89	PL N = 90
Age (years)								
Mean (SD)	64.1 (8.3)	64.6 (7.6)	63.3 (8.1)	61.5 (8.2)	61.5 (8.9)	65.5 (9.5)	67.8 (7.3)	65.4 (8.4)
Range	41 to 87	43 to 82	41 to 81	42 to 79	41 to 87	41 to 84	49 to 84	40 to 82
Male, n (%)	84 (64.1)	63 (82.9)	61 (69.3)	69 (77.5)	70 (76.9)	64 (69.6)	51 (57.3)	55 (61.1)
Caucasian, n (%)	128 (97.7)	75 (98.7)	87 (98.9)	89 (100.0)	91 (100.0)	89 (96.7)	88 (98.9)	85 (94.4)
Smoking history, n (%)								
Never	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ex-smoker	80 (61.1)	48 (63.2)	50 (56.8)	51 (57.3)	48 (52.7)	64 (69.6)	56 (62.9)	56 (62.2)
Smoker	50 (38.2)	28 (36.8)	38 (43.2)	38 (42.7)	43 (47.3)	28 (30.4)	33 (37.1)	34 (37.8)
Pack-years								
Mean (SD)	59.9	35.5 (16.1)	43.4 (25.8)	42.7 (26.1)	41.8 (23.8)	60.0 (32.1)	54.0 (21.9)	60.0 (33.0)
Range	15 to 300	11 to 91	11 to 135	11 to 195	10 to 121	10 to 171	15 to 135	20 to 200
COPD duration (years)								
Mean (SD)	9.7 (8.4)	11.4 (7.1)	10.4 (7.7)	9.9 (6.8)	9.7 (7.5)	10.3 (7.3)	9.7 (6.4)	8.6 (6.8)
Range	0.2 to 68	1.5 to 32	0.7 to 46	0.3 to 29	0.3 to 42	0.4 to 32.5	1 to 30	0.3 to 36
Screening Lung Function[a]								
FEV_1 (L)								
Mean	1.011	1.121	1.195	1.324	1.279	1.015	0.990	1.116
Range	0.28 to 2.18	0.40 to 2.34	0.52 to 1.98	0.46 to 2.17	0.53 to 2.28	0.35 to 2.42	0.31 to 1.98	0.41 to 1.89
% predicted normal FEV_1								
Mean	35.8	39.6	42.9	44.9	43.8	36.7	37.9	40.5
Range	14.9 to 59.2	16.8 to 61.4	19.3 to 66.9	12.7 to 64.3	20.3 to 64.2	10 to 60.7	15.1 to 60.2	12.6 to 60.1
FEV_1/FVC ratio (%)								
Mean	45.1	37.8	48.9	51.3	50.5	44.6	45.2	45.5
Range	24.7 to 68.9	23.7 to 60.2	27.2 to 70.7	15.4 to 72.1	26.0 to 81.3	19.8 to 64.3	19.2 to 68.5	20.5 to 67.8

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; Iprat 36 = ipratropium 36 mcg four times daily dose; L = litre; No. = number; PL = placebo; SD = standard deviation; Tio R 5 = Spiriva Respimat 5 mcg daily dose.

[a] Screening lung function data are pre-bronchodilator.

Source: Clinical Study Report (CSR) 205.249,[1] CSR 205.250,[2] CSR 205.251,[3] CSR 205.252,[12] CSR 205.254,[4] and CSR 205.255.[5]

TABLE 6B: SUMMARY OF BASELINE CHARACTERISTICS (CONTINUED)

Characteristic	Study No. and Treatment							
	205.254		205.255		205.372		205.452 (TIOSPIR)	
	Tio R 5 N = 332	PL N = 319	Tio R 5 N = 338	PL N = 334	Tio R 5 N = 1,952	PL N = 1,965	Tio R 5 N = 5,705	Tio H 18 N = 5,687
Age (years)								
Mean (SD)	65.0 (8.2)	64.7 (8.9)	64.4 (8.9)	65.7 (8.4)	64.8 (9.1)	64.8 (9.0)	64.9 (9.1)	65.0 (9.0)
Range	42 to 90	40 to 87	38 to 85	41 to 87	40 to 88	40 to 91		
Male, n (%)	243 (73.2)	252 (79.0)	248 (73.4)	235 (70.4)	1,524 (78.1)	1,513 (77.0)	4,134 (72.5)	4,035 (71.0)
Caucasian, n (%)	304 (91.6)	292 (91.5)	307 (90.8)	302 (90.4)	1,343 (68.8)	1,346 (68.5)	4,650 (81.5)	4,630 (81.4)
Smoking history, n (%)								
Never	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)	0 (0)	1 (0)	1 (0)
Ex-smoker	208 (62.7)	217 (68.0)	208 (61.5)	200 (59.9)	1,254 (64.2)	1,260 (64.1)	3,496 (61.3)	3,542 (62.3)
Smoker	124 (37.3)	102 (32.0)	130 (38.5)	134 (40.1)	697 (35.7)	705 (35.9)	2,208 (38.7)	2,144 (37.7)
Pack-years								
Mean (SD)	46.8 (28.6)	45.8 (25.4)	47.4 (25.1)	49.3 (26.7)	46.0 (26.1)	44.98 (26.5)	44.1 (25.0)	43.7 (24.7)
Range	10 to 250	11 to 180	10 to 250	10 to 180	10 to 200	0.5 to 260	NR	NR
COPD duration (years)								
Mean (SD)	8.6 (6.5)	9.9 (8.1)	8.1 (6.4)	9.0 (6.8)	8.3 (7.0)	8.1 (6.5)	7.4 (6.2)	7.5 (6.2)
Range	0 to 33.0	0.1 to 43.0	0 to 35.8	0 to 44	0.1 to 51	0 to 56	NR	NR
Screening Lung Function[a]								
FEV_1 (L)								
Mean	1.067	1.087	1.109	1.079	1.097	1.088	1.352	1.338
Range	0.36 to 2.27	0.16 to 2.44	0.25 to 2.78	0.36 to 2.37	0.23 to 2.61	0.30 to 2.67	NR	NR
% predicted normal FEV_1								
Mean	38.3	37.8	39.2	38.8	39.86	39.83	48.5	48.4
Range	11.9 to 61.3	5.5 to 59.8	9.6 to 83.5	13.3 to 84.5	7.0 to 84.7	11.3 to 64.4	NR	NR
FEV_1/FVC ratio (%)								
Mean	42.9	43.1	43.0	42.4	47.2	46.7	50.1	49.8
Range	17.7 to 82.7	15.8 to 84.2	18.4 to 76.3	18.8 to 82.3	13.7 to 96.6	17.4 to 95.4	NR	NR

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; Iprat 36 = ipratropium 36 mcg four times daily dose; L = litre; No. = number; NR = not reported; PL = placebo; SD = standard deviation; Tio R 5 = Spiriva Respimat 5 mcg daily dose; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose.

[a] Screening lung function data are pre-bronchodilator except for Study 205.452 (TIOSPIR), which was reported only as post-bronchodilator.

Source: Clinical Study Report (CSR) 205.254,[4] CSR 205.255,[5] CSR 205.372,[13] and CSR 205.452.[14]

One purpose of TIOSPIR was to establish that, compared with tiotropium administered through the HandiHaler, tiotropium administered through the Respimat device has similar effects on mortality. As detailed in Table 7, the medical history of patients randomized into Study 205.452 appeared to be well balanced between the two treatment groups. The majority (> 92%) of patients did not have heart failure, and more than 50% of patients had not had a COPD exacerbation requiring treatment in the past year, possibly due to use of effective pulmonary medications. Concomitant use of CV medication at baseline also appeared to be well balanced between the treatment groups, as shown in Table 8.

TABLE 7: STUDY 205.452 (TIOSPIR) MEDICAL HISTORY OF RANDOMIZED PATIENTS (TREATED SET)

Medical History	Treatment, n (%)	
	Tio R 5 (N = 5,705)	Tio H 18 (N = 5,687)
Stroke	139 (2.4)	125 (2.2)
TIA	98 (1.7)	74 (1.3)
MI	339 (5.9)	347 (6.1)
Ischemic heart disease or coronary artery diseases	855 (15.0)	893 (15.7)
Cardiac arrhythmia	614 (10.8)	607 (10.7)
Atrial fibrillation or flutter	232 (4.1)	222 (3.9)
Ventricular fibrillation	9 (0.2)	9 (0.2)
Supraventricular tachycardia	51 (0.9)	58 (1.0)
Ventricular tachycardia	25 (0.4)	27 (0.5)
Bradycardia	62 (1.1)	74 (1.3)
Atrioventricular block	32 (0.6)	48 (0.8)
Bundle branch block	145 (2.5)	137 (2.4)
Other conduction disorder	125 (2.2)	117 (2.1)
Heart Failure Class		
None	5,259 (92.2)	5,251 (92.3)
Class I	184 (3.2)	153 (2.7)
Class II	226 (4.0)	246 (4.3)
Class III	31 (0.5)	32 (0.6)
Class IV	2 (0.0)	3 (0.1)
Missing	3 (0.1)	2 (0.0)
No. COPD Episodes Treated in Last Year		
0	2,965 (52.0)	2,947 (51.8)
1	1,587 (27.8)	1,647 (29.0)
2	705 (12.4)	666 (11.7)
3	265 (4.6)	258 (4.5)
4	106 (1.9)	103 (1.8)
5 or more	73 (1.3)	64 (1.1)
Missing	4 (0.1)	2 (0.0)
Ever Breathless		
No	173 (3.0)	202 (3.6)
Yes (MMRC Scale)	5,525 (96.8)	5,480 (96.4)
0	310 (5.6)	283 (5.2)
1	2,113 (38.2)	2,130 (38.9)
2	2,067 (37.4)	2,062 (37.6)

Medical History	Treatment, n (%)	
	Tio R 5 (N = 5,705)	Tio H 18 (N = 5,687)
3	940 (17.0)	887 (16.2)
4	95 (1.7)	118 (2.2)
Missing	0 (0.0)	0 (0.0)
Missing	7 (0.1)	5 (0.1)
Sputum-producing cough > 3 month for 2 years	3,614 (63.4)	3,608 (63.5)

COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; MMRC = Modified Medical Research Council; TIA = transient ischemic attack; Tio R 5 = Spiriva Respimat 5 mcg daily dose; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; TS = treated set.
Source: Clinical Study Report 205.452.[14]

TABLE 8: STUDY 205.452 (TIOSPIR) CONCOMITANT USE OF CARDIOVASCULAR THERAPY AT BASELINE (TREATED SET)

	Treatment, n (%)	
Cardiovascular Therapy	Tio R 5 (N = 5,705)	Tio H 18 (N = 5,687)
Total taking cardiac medication	2,903 (50.9)	2,890 (50.8)
Beta blockers	805 (14.1)	831 (14.6)
Calcium channel blockers	1,035 (18.1)	981 (17.2)
Cardiac glycosides (Digoxin)	95 (1.7)	86 (1.5)
ACE inhibitors	1,196 (21.0)	1,147 (20.2)
Angiotensin receptor blockers	663 (11.6)	629 (11.1)
Nitrates	239 (4.2)	239 (4.2)
Antiarrhythmics class I or III (sodium channel blockers) or potassium channel blockers)	63 (1.1)	77 (1.4)
Adenosine	7 (0.1)	4 (0.1)
Acetylsalicylic acid	1,098 (19.2)	1,122 (19.7)
Anticoagulants vitamin K antagonists	149 (2.6)	139 (2.4)
Anticoagulants direct thrombin inhibitors	24 (0.4)	30 (0.5)
Anticoagulants factor Xa inhibitors	4 (0.1)	15 (0.3)
Antiplatelets	222 (3.9)	208 (3.7)

ACE = angiotensin-converting enzyme; Tio R 5 = Spiriva Respimat 5 mcg daily dose; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; TS = treated set.
Source: Clinical Study Report 205.452.[14]

Almost all included patients were using pulmonary medication at baseline (i.e., approximately 82% to 99%) as per Table 9. Most patients were using beta-2 agonists at baseline, although in studies 205.254 and 205.255, the use of LABAs was somewhat lower (28% to 31%) compared with the other trials (41% to 62%). In Study 205.252 there appeared to be a disproportionately higher use of SABAs (79.3%) compared with the other trials (approximately 52% to 55%). In all studies, with the exception of studies 205.372 and TIOSPIR, patients who had previously received tiotropium through participation in a clinical trial or commercially available tiotropium (Spiriva) were excluded. In Study 205.372, 13.2% of patients had received tiotropium previously, and in Study 205.452, 46.9% of patients had received prior tiotropium. Few patients had used xanthines, with the exception of Study 205.251 where 33.8% of patients were reported to have used xanthines at baseline.

TABLE 9: CONCOMITANT USE OF PULMONARY MEDICATION AT BASELINE (WITHIN TWO MONTHS OF SCREENING VISIT)

	Study No., n (%)							
Prior COPD Medication	205.249 (N = 131)	205.250 (N = 76)	205.251 (N = 361)	205.252 (N = 358)	205.254 (N = 983)	205.255 (N = 1,007)	205.372 (N = 3,917)	205.452 N = 17,116
≥ 1 pulm. med.	115 (87.8)	75 (98.7)	311 (86.1)	321 (89.7)	844 (85.9)	821 (81.5)	3,319 (84.7)	15,500 (90.6)
Beta-agonist	112 (85.5)	74 (97.4)	-	-	-	-	-	-
LABA	NR	NR	152 (42.1)	147 (41.1)	277 (28.2)	310 (30.8)	2,082 (53.2)	1,0578 (61.8)
SABA	NR	NR	200 (55.4)	284 (79.3)	521 (53.0)	548 (54.4)	2,049 (52.3)	9,174 (53.6)
Oral	NR	NR	4 (1.1)	2 (0.6)	4 (0.4)	11 (1.1)	117 (3.0)	351 (2.1)
Anticholinergics[a]	78 (59.5)	58 (76.3)	-	-	-	-	-	-
SAMA	NR	NR	77 (21.3)	105 (29.3)	296 (30.1)	209 (20.8)	483 (12.3)	2,963 (17.3)
LAMA	NR	NR	NA	NA	1 (0.1)	1 (0.1)	519 (13.2)	8,023 (46.9)
Combinations	60 (45.8)	47 (61.8)	111 (30.7)	207 (57.8)	309 (31.4)	386 (38.3)	2,111 (53.9)	NR
SAMA/LABA	NR	NR	49 (13.6)	132 (36.9)	181 (18.4)	217 (21.5)	522 (13.3)	NR
ICS/LABA	NR	NR	62 (17.2)	75 (20.9)	128 (13.0)	169 (16.8)	1,589 (40.6)	8,872 (51.8)
Steroids[b]	57 (43.5)	66 (86.8)	-	-	-	-	-	-
Inhaled	NR	NR	175 (48.5)	185 (51.7)	511 (52.0)	557 (55.3)	2,205 (56.3)	10,103 (59.0)
Oral	NR	NR	33 (9.1)	13 (3.6)	27 (2.7)	34 (3.4)	101 (2.6)	804 (4.7)
IV/IM	NR	NR	NR	1 (0.3)	NR	1 (0.1)	2 (0.1)	NR
Xanthines	7 (5.3)	4 (5.3)	122 (33.8)	29 (8.1)	183 (18.6)	114 (11.3)	904 (23.1)	2,671 (15.6)
Antibiotics	3 (2.3)	NR	NR	NR	8 (0.8)	11 (1.1)	53 (1.4)	NR
Mucolytics	NR	22 (28.9)	31 (8.6)	NR	62 (6.3)	17 (1.7)	360 (9.2)	1,239 (7.2)
Oxygen	3 (2.3)	NR	3 (0.8)	9 (2.5)	14 (1.4)	12 (1.2)	63 (1.6)	700 (4.1)

COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroids; IM = intramuscular; IV = intravenous; LABA = long-acting beta-2 agonist; LAMA = long-acting muscarinic antagonist NA = not applicable; No. = number; NR = not reported; pulm med = pulmonary medicine; SABA = short-acting beta-2 agonist; SAMA = short-acting muscarinic receptor antagonist.

[a] In studies 205.249, 205.250, 205.251, 205.252, 205.254, and 205.255, patients with prior use of tiotropium were excluded from these trials, whereas they were not excluded from studies 205.372 and 205.452.

[b] In Study 205.452, oral and IV/IM steroids were combined and not reported separately.

Note: Data are for the total study populations (including Tio R 2.5 mcg and Tio R 10 mcg groups), as results were not reported separately.

Source: Clinical Study Report (CSR) 205.249,[1] CSR 205.250,[2] CSR 205.251,[3] CSR 205.252,[12] CSR 205.254,[4] CSR 205.255,[5] CSR 205.372,[13] and CSR 205.452.[14]

The use of combined ICS/LABA at baseline was much higher in Study 205.372 (40.6%) and Study 205.452 (51.8%) compared with the previous trials (13.0% to 20.9%), as detailed in Table 9 and Table 10.

TABLE 10: STUDY 205.452 (TIOSPIR) CONCOMITANT USE OF ICS AND/OR LABA AT BASELINE (TS)

COPD Medication	Treatment, n (%)	
	Tio R 5 N = 5,705	Tio H 18 N = 5,687
ICS, LABA, or Both		
ICS (but not LABA)	403 (7.1)	424 (7.5)
LABA (but not ICS)	542 (9.5)	587 (10.3)
Both ICS and LABA	2,949 (51.7)	2,956 (52.0)
Neither (ICS nor LABA)	1,811 (31.7)	1,720 (30.2)

COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroids; LABA = long-acting beta-2 agonist; Tio R 5 = Spiriva Respimat 5 mcg daily dose; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; TS = treated set.
Source: Clinical Study Report 205.452.[14]

3.2.3 Interventions

Patients were trained on the proper use (i.e., priming, oral inhalation) of the Respimat, HandiHaler, and MDI devices at the screening and randomization visits. In addition, patients were instructed on how to use the devices at home. During study visits, study personnel observed the patients' technique when inhaling the study medication.

Open-label salbutamol MDI was available as rescue medication in all included trials. Patients were to record the number of occasions of rescue medication use on their diary card. If rescue medication was administered during a spirometry test day, the patient was not permitted to complete the remainder of the test day.

Across all trials, if a patient suffered an acute COPD exacerbation, the following mediations were permitted as medically necessary: salbutamol MDI as required, temporary increases in dose or addition of theophylline and/or oral steroids, and antibiotics. In Study 205.452, in the case of potentially life-threatening COPD exacerbations, it was stated that any and all therapies and interventions deemed medically necessary by the treating physician could be prescribed.

In studies 205.249 and 205.250, Tio R 5, Tio H 18, and placebo were administered once daily in the morning (between 7:00 a.m. and 10:00 a.m. in a double-dummy design with tiotropium or placebo inhalation solution through the Respimat inhaler (two actuations) followed by inhalation of the powder capsule content (tiotropium or placebo) through the HandiHaler device. During the four randomized treatment periods, all bronchodilators were discontinued and replaced with study medication and open-label salbutamol MDI as needed. Some medications, including oral and ICS, mucolytic agents, and salbutamol, were allowed during the studies if the patient had been stabilized for at least six weeks prior to and during the study. Inhaled SABAs or LABAs were allowed during the washout periods, but were not permitted for eight hours and 48 hours, respectively, prior to clinic visits; short-acting theophylline could be used as long as there was a 24-hour washout period prior to clinic visits.

In studies 205.251 and 205.252, study drugs were administered in a double-dummy design with Tio R 5, TIO R 10, or placebo inhalation solution by the Respimat inhaler once daily in the morning (between 7:00 a.m. and 10:00 a.m.) and ipratropium bromide (36 mcg; two actuations of 18 mcg) or placebo MDI taken four times daily at appropriately spaced intervals (i.e., morning, mid-day, early evening, and

before bed). Similar to the previous studies, permitted medications (if stabilized for at least six weeks prior to and throughout the study period) included oral and ICS, theophylline, mucolytic agents, salbutamol, and antileukotrienes and leukotriene receptor antagonists, only if prescribed for conditions other than asthma or excluded allergic conditions. Patients using fixed-dose ICS/LABA combinations had to be switched to the ICS monotherapy at least 48 hours prior to the randomization visit without a change in corticosteroid dose. Medications not allowed during the treatment period were anticholinergic drugs other than the study drug, SABAs (other than rescue salbutamol), orally inhaled LABAs (formoterol, salmeterol), fixed-dose combination anticholinergic/beta-adrenergic therapies (e.g., Combivent, Duovent), and fixed-dose combination ICS/LABAs (e.g., Advair, Symbicort).

In studies 205.254 and 205.255, patients were randomized to one of three treatment groups: Tio R 5, Tio R 10, or placebo. Each patient self-administered two inhalations from the Respimat inhaler (tiotropium or placebo) once daily in the morning (between 7:00 a.m. and 10:00 a.m.). Excluded medications during the treatment period were identical to those excluded in studies 205.251 and 205.252.

Study 205.372 differed from the previous trials in that patients were allowed to continue their usual maintenance COPD treatment (e.g., ICS, low dose [< 10 mg] oral steroids, methylxanthines, SABAs and LABAs [alone or in combination with ICS] as concomitant medications in this study, whereas they had not been permitted do so to in the previous studies. In contrast to the earlier trials, patients who had previously received tiotropium were eligible for entry into the trial provided they had undergone adequate washout. The only medications that were excluded during the treatment period were anticholinergic bronchodilators other than study drug. Patients self-administered Tio R 5 or placebo each morning at approximately the same time of day upon awakening, with the exception of the mornings of clinic visits requiring performance of lung function measurements. All medications used throughout the trial were recorded using electronic Case Report Forms (CRFs).

In TIOSPIR, all patients randomized into the DB portion of the study received one of three tiotropium treatments (i.e., either one of two tiotropium doses [2.5 mcg or 5.0 mcg] delivered through the Respimat or 18 mcg delivered through the HandiHaler). The order of inhalation from the two devices was fixed and was the same for all patients (i.e., inhalation from the HandiHaler first and then from the Respimat 30 seconds to one minute later). The only concomitant medications that were excluded during the randomized treatment period were inhaled short- and long-acting anticholinergic drugs.

3.2.4 Outcomes

a) Chronic Obstructive Pulmonary Disease Exacerbations

In general, in the trials that included COPD exacerbations as an outcome (i.e., studies 205.254, 205.255, 205.372, and TIOSPIR), a COPD exacerbation was defined as “a complex of respiratory events/symptoms with a duration of three days or more requiring a change in treatment.” A complex of respiratory events/symptoms meant two or more of the following (increase of symptom or new onset): shortness of breath/dyspnea/shallow, rapid breathing, sputum production (volume), occurrence of purulent sputum, cough, wheezing, and chest tightness. The change in or requirement of treatment included the prescription of antibiotics and/or systemic corticosteroids and/or or a significant change of the prescribed respiratory medication (bronchodilators including theophylline). The onset of an exacerbation was defined by the onset of the first recorded symptom. The end of the exacerbation was to be recorded as defined by the investigator.

In studies 205.254 and 205.255, the effect of tiotropium on COPD exacerbations was primarily determined by the number of COPD exacerbations (defined as a complex of respiratory events reported

as AEs with a duration of three days or more requiring treatment with antibiotics and/or oral corticosteroids) occurring in a year. The number of COPD exacerbations that occurred over the 48-week treatment period was one of four co-primary end points in these trials. Information on COPD exacerbations, including details of treatments given and hospitalizations, were collected on the CRF. Data were not reported for COPD exacerbations by individual trial; therefore, only combined results for COPD exacerbations from studies 205.254 and 205.255 are available, as reported in Table 34.[15]

In Study 205.372, the time to first COPD exacerbation was one of two co-primary end points. COPD exacerbations were defined identically as in previous trials. In addition, exacerbations were further categorized as mild (treated at home without seeing a health care provider), moderate (visit with health care provider; e.g., home visit, visit to an outpatient facility or an emergency department but not requiring admission to hospital), or severe (hospitalization; i.e., an emergency department stay longer than 24 hours).

In TIOSPIR, one of two co-primary end points was the time to first COPD exacerbation (efficacy end point). COPD exacerbations were defined as in previous trials, as was the onset and end of an exacerbation. Data on COPD exacerbations were captured on a COPD exacerbation electronic CRF (eCRF). Exacerbations were classified as mild (a new prescription of maintenance bronchodilator only), moderate (antibiotics or systemic steroids without hospitalization), and severe (hospitalization).

b) Quality of Life

In studies 205.254, 205.255, and 205.372, the effect of tiotropium on patient's health status was primarily determined by the total score from the SGRQ, which is a standardized, self-administered instrument for measuring impaired health and perceived well-being in respiratory disease. Details on the SGRQ are provided in Table 61. The SGRQ contains 50 items divided into three dimensions: symptoms (measuring distress due to respiratory symptoms), activity (measuring the effect of disturbances on mobility and physical activity) and impacts (measuring the psychosocial impact of the disease). Total SGRQ scores range from 0 to 100, with higher values indicating lower health-related quality of life (HRQoL). A score of 0 indicates no impairment of QoL. The minimal clinically important difference (MCID) has been reported to be an improvement of at least four units in the SGRQ total score. Negative changes in scores indicate improvement in HRQoL. The between-treatment differences in SGRQ total score was one of four co-primary end points in studies 205.254 and 205.255, and was a secondary end point in Study 205.372. The SGRQ was administered at the end of the run-in period and after eight, 16, 32, and 48 weeks of treatment; it was also administered after three weeks off treatment in studies 205.254 and 205.255 and after 24 and 48 weeks off treatment in Study 205.372.

c) Pulmonary Function Measurements

In studies 205.249, 205.250, 205.251, and 205.252, the primary efficacy end point was the trough FEV_1 response determined at the end of the treatment period. Trough FEV_1 response is defined as the change from baseline in trough FEV_1 at the end of the dosing interval. Baseline FEV_1 is the pre-treatment FEV_1 measured at test day 1 of each treatment period in the morning 10 minutes prior to the administration of the first dose of study medication. Trough FEV_1 is defined as the FEV_1 measured at the –10 minutes time point at the end of the dosing interval 24 hours post-drug administration on the last day of treatment. The MCID is reported to be a change of 0.100 L to 0.140 L, as detailed in Table 61.

In studies 205.254 and 205.255, the trough FEV_1 response at the end of the 48-week treatment period was one of four co-primary end points. In Study 205.372, trough FEV_1 response at 48 weeks was one of two co-primary efficacy end points. Trough FEV_1 response in these trials was defined as in the previous

trials. In Study 205.452, trough FEV_1 was reported in a subset of patients in the SSS (i.e., 461 patients treated with Tio R 5 and 445 patients treated with Tio H 18).

d) Chronic Obstructive Pulmonary Disease Symptoms

In studies 205.251, 205.252, 205.254, and 205.255, the severity of COPD symptoms (i.e., wheezing, shortness of breath, coughing, and tightness of chest) were recorded on the CRFs at the end of the run-in period (visit 2) and at each visit thereafter. The scores were based on the investigator's assessment of the patient's condition during the week just prior to the visit and evaluated prior to the conduct of pulmonary function tests using a scale where 0 = none, 1 = mild, 2 = moderate, and 3 = severe symptoms.

e) Transition Dyspnea Index

In studies 205.254 and 205.255, the effect of tiotropium on dyspnea was primarily assessed using the Mahler Baseline Dyspnea Index (BDI) and transitional dyspnea index (TDI) focal score, which is the sum of the three components of the TDI (i.e., functional impairment, magnitude of task, and magnitude of effort). The BDI domains are rated from 0 (severe) to 4 (unimpaired), and the rates are summed for the baseline focal score ranging from 0 to 12; the lower the score, the worse the severity of dyspnea. The TDI domains are rated from –3 (major deterioration) to 3 (major improvement), and the rates are summed for the transition focal score ranging from –9 to 9; negative scores indicate deterioration. Thus, the BDI measured the severity of dyspnea at the beginning of the study and the TDI evaluated changes from the BDI at different time points. The MCID for the TDI focal score has been reported to be an improvement of at least one unit from the BDI, as detailed in Table 61. The TDI focal score at the end of the 48-week treatment period was one of four co-primary end points in these trials. The BDI was performed at the randomization visit, and the TDI was performed at week 8 and at eight-weekly intervals until the end of treatment.

f) Rescue Medication Use

In all studies the permitted rescue medication was salbutamol MDI on an as-needed basis and use was self-reported by patients on diary cards.

g) Patient Adherence and Satisfaction

Treatment compliance was assessed based on each patient's recordings on diary cards of study medication taken and the number of occasions of salbutamol MDI use. The investigator reviewed these records with the patient at each study visit to assess treatment compliance. In addition, patients were to return all dispensed Respimat inhalers and cartridges, capsules (used and unused), HandiHaler devices, and salbutamol MDIs to the clinic. During pulmonary function test days, study personnel supervised the inhalation of study medication by patients.

In Study 205.252, a patient satisfaction and preference questionnaire was administered at the end of treatment (at US sites only).

h) Safety Assessments

Safety outcomes reported in all studies were all-cause mortality, treatment-emergent AEs, SAEs, and WDAEs. In Study 205.452, one of two co-primary end points (safety) was death due to any cause. The primary cause of each death in the study was independently assessed under blinded conditions by a Mortality Adjudication Committee. TIOSPIR also included an analysis of major adverse cardiovascular events (MACE), which was defined as a fatal event in the system organ class of cardiac and vascular disorders, of which preferred terms were sudden death, cardiac death, sudden cardiac death, as well as

outcome events of myocardial infarction (MI), stroke and transient ischemic attacks (TIAs) (all serious and non-serious events). Further safety end points were time to onset of first stroke or MI or TIA.

Outcomes included in the study protocol for which there were no outcome data available include health care utilization, exercise tolerance, and days of missed school or work.

3.2.5 Statistical Analysis

Studies 205.249 and 205.250 had identical protocols that specified a priori that analyses would be performed for the individual studies as well as on the combined data, including all sites. According to the manufacturer, based on unspecified previous studies, the standard deviation (SD) for paired differences in trough FEV_1 was assumed to be 0.12 L, and a mean difference of 0.05 L was considered by the manufacturer to be clinically meaningful. The expected difference between active and placebo treatment was 0.13 L. Given these assumptions and using a one-sided alpha = 0.025, a total of 64 patients were required to demonstrate non-inferiority to within 0.05 L in trough FEV_1 for a single comparison with approximately 90% power and a type I error probability of 2.5% (one-sided) using a t-test for paired differences. Of the four ordered primary comparisons, two were to show efficacy versus placebo and two were to show non-inferiority to Tio H 18 with a pre-specified non-inferiority margin of 0.05 L. With a sample of 64 evaluable patients, the powers for detecting a difference of 0.13 L and excluding a difference of 0.05 L at the 2.5% level of significance (one-sided) were > 99% and 90%, respectively. Because the four comparisons are not independent, the overall power for this sample size was between 80% and 90%.

As there were two objectives in these studies (i.e., to demonstrate superiority versus placebo and non-inferiority to the HandiHaler at the end of each four-week treatment period), the comparisons were conducted in a closed stepwise procedure using the FAS. The first and second steps were to test the superiority of each of Tio R 10 and then Tio R 5 versus placebo, and then the third and fourth were to test the non-inferiority of each of Tio R 10 and Tio R 5 to Tio H 18. Each step was considered confirmatory only if all previous steps were successful. The statistical model was analysis of covariance (ANCOVA) with terms for centre, patients within centre, period, baseline, and treatment. Superiority between each of Tio R 10 and Tio R 5 and placebo was concluded if the lower limit of the 95% CI for the difference in adjusted mean trough FEV_1 response did not include 0. Non-inferiority between each of Tio R 10 and Tio R 5 and Tio H 18 was concluded if at a [one-sided] $P < 0.025$, the lower bound of the 95% CI for the absolute difference in trough FEV_1 was above –0.50 L, the pre-specified non-inferiority margin. Confirmatory analyses were conducted using the per-protocol (PP) set. No subsequent test for superiority was pre-specified. In the event of missing trough FEV_1 values, the lowest value recorded on the first test day was used instead (even if it was the baseline value).

Studies 205.251 and 205.252 also had identical protocols that specified a priori that analyses would be conducted on the individual studies, as well as on the combined data. According to the manufacturer, based on unspecified previous studies, the SD for trough FEV_1 was assumed to be 0.215 L. Of the six planned comparisons, four were to detect a difference in trough FEV_1 of 0.13 L, and two were to detect a difference of 0.18 L. With a sample of 280 evaluable patients (70 per treatment group), the powers for detecting differences of 0.13 L and 0.18 L at the 2.5% level of significance (one-sided) are 94% and 99%, respectively. However, because these comparisons were not independent, the overall power for this sample size was between 77% and 94%.

The primary efficacy comparison was designed to demonstrate the bronchodilatory superiority of tiotropium inhalation solution to placebo, then its non-inferiority to ipratropium inhalation aerosol, and finally its superiority to ipratropium inhalation aerosol at 12 weeks. The analysis was to be conducted in

a stepwise procedure, with each dose of tiotropium inhalation solution compared with the specified control before moving to the subsequent control comparison. The primary analysis was an ANCOVA comparing the bronchodilatory efficacy of each of the four treatments with terms for smoking status, centre, and treatment. Each hypothesis test was performed at alpha = 0.025 (one-sided). Superiority of Tio R 5 and Tio R 10 to placebo was to be first demonstrated by the mean FEV_1 response for tiotropium being greater than the placebo response. Next, non-inferiority of Tio R 5 or Tio R 10 to ipratropium was concluded if at a (one-sided) $P < 0.025$, the lower bound of the 95% CI for the absolute difference in trough FEV_1 was above –0.50 L, the pre-specified non-inferiority margin. There was no PP analysis in these studies. If the non-inferiority criterion was achieved, the superiority of Tio R 5 or Tio R 10 to ipratropium for trough FEV_1 could then be tested at a two-sided alpha = 0.05. In the event of missing values, they were to be estimated using other values recorded for the patient on that test day. For patients with missing data on a given test day because rescue medication had been taken, the missing data were to be estimated by the least favourable observation on that test day (even if it was a pre-dose value). For patients discontinuing the study early due to unexpected worsening of COPD, the missing data were to be imputed by the least favourable data prior to discontinuation. The missing data for those patients who missed a visit due to other reasons were to be estimated by their last observed data.

Studies 205.254 and 205.255 were also identical, each having four co-primary end points and protocols that specified a priori that the first two end points (trough FEV_1 response and SGRQ total score) would be analyzed by individual study and that the latter two end points (TDI focal score and COPD exacerbations) would be analyzed by combining the data from the two studies. The analyses were conducted on results after 48 weeks of treatment. According to the manufacturer, based on unspecified previous studies, the SD for trough FEV_1 was assumed to be 0.215 L. Therefore, a sample of 810 patients (270 per treatment group) was considered by the manufacturer to be adequate to detect a difference of 0.13 L in mean trough FEV_1 response between tiotropium and placebo at the 5% level of significance with at least 99% power using a two-tailed t-test. The combined analysis of 1,620 evaluable patients (540 per treatment group) had at least 95% power to detect a difference of 0.05 L in mean trough FEV_1 response between the two doses of tiotropium at the 5% level of significance (two-sided). In the combined data, 272 patients per treatment group were adequate to detect a difference in the mean TDI focal score of one unit between treatments with 90% power at the 5% significance level using a two-tailed t-test. In the combined data, 270 patients per treatment group was adequate to detect a difference of four points in mean SGRQ total score between treatments with 96% power at the 5% level of significance using a two-tailed t-test. Based on recent studies conducted over six months across Europe and the US, the SD for the number of COPD exacerbations in one year was assumed to be 2.4 and the expected mean difference was assumed to be 0.4. Therefore, the pooled sample of 1,620 patients (540 per treatment group) was adequate to detect a significant difference between treatments, with a 5% level of significance (two-sided) and 76% power using the Wilcoxon–Mann–Whitney test. The power estimates described above assumed that all previous steps had been statistically significant.

In the analyses of the four co-primary end points, the family-wise type I error rate was controlled at 5% by testing the end points in the following order: trough FEV_1 response (by study), SGRQ total score (by study), Mahler TDI focal score (combined), and COPD exacerbations (combined). A dose (i.e., Tio R 5 or Tio R 10) for an end point was tested only if the dose was shown to have had significant efficacy for all previous end points. In order to progress to testing the Mahler TDI, the dose must have shown statistical significance for the FEV_1 response and the SGRQ (total score) for both studies. All tests were conducted as two-tailed at the 5% level of significance. Missing values for spirometry measures were to be estimated using other values recorded for the patient on that test day. For patients with missing data on a given test day because rescue medication had been taken, the missing data were to be estimated by

the least favourable observation on that test day (even if it was a pre-dose value). Missing SGRQ data were to be imputed by the last observation carried forward (LOCF) rule, to be consistent with the method used in the validation of the questionnaire.

In Study 205.372, the sample size was based on being able to claim superiority of Tio R 5 over placebo in terms of the change from baseline in trough FEV_1 after 48 weeks of treatment and the time to first COPD exacerbation during the 48-week randomized treatment period. Data from studies 205.254 and 205.255 supported that the SD for the trough FEV_1 was 0.229 L. Therefore, a sample size of 3,000 patients (1,500 patients per treatment group) was considered by the manufacturer to be adequate to detect a difference of 0.13 L in mean change from baseline trough FEV_1 between Tio R 5 and placebo at the 5% level of significance (two-sided) with at least 99% power. Data from the same studies showed that 44.1% of placebo patients experienced at least one COPD exacerbation compared with 37.2% of Tio R 5 treated patients, resulting in a HR of 0.800 (20.0% reduced risk). A sample size of 3,000 patients (1,500 patients per treatment group) would have been adequate to detect this HR with a power of 97%. However, it is known that LABA use is likely to dilute any treatment effect; therefore, the HR for this study was expected to be larger. With a sample size of at least 3,000 patients (1,500 patients per treatment group) a 0.050 level two-sided log-rank test for equality of survival curves had 80% power to detect a constant HR of approximately 0.850 (15% reduced risk), assuming the proportion of patients experiencing at least one exacerbation was 37.2% for Tio R 5 and 42.1% for placebo.

The two co-primary end points in Study 205.372 were analyzed differently; however, they were tested in a stepwise manner to protect overall type I error. The change in trough FEV_1 was analyzed first using ANCOVA including terms for centre (fixed), LABA use, and treatment, and baseline trough FEV_1 as a covariate. If superiority of Tio R 5 over placebo was established, the treatment groups were compared for time to first COPD exacerbation, which was analyzed using Cox's proportional hazards regression model including terms for centre, LABA use, and treatment. Only COPD exacerbations with onset during randomized treatment were included in the analysis. Missing spirometry measurements (post-baseline) and missing SGRQ data were imputed using the LOCF technique.

In TIOSPIR, the sample size was based on both co-primary end points and on results from the UPLIFT trial.[8,9] For the end point of all-cause deaths, assuming a one-sided significance level of 2.5%, death rate of 5.6% at two years, accrual of 1.5 years, maximum follow-up of 3.5 years, lost to follow-up rate of ≤ 1%, and a non-inferiority HR margin of 1.25, the number of events required for the two group comparison was 844 with 90% power. The number of patients was 5,587 per group (rounded to 5,600) and because the trial had three treatment groups, the minimum number of fatal cases needed was 1,266 and the estimated number of patients needed was 16,800. For the end point of time to first COPD exacerbation, given a sample size of 5,600 per group, a 60% exacerbation rate for Tio H 18, a length of accrual of 1.5 years, a maximum follow-up of 3.5 years, a lost to follow-up rate of 35%, and a two-sided significance level of 5%, the trial was projected to be able to detect an 8% hazard reduction in COPD exacerbations with Tio R 5 with 90% power. The sample size for the SSS was estimated to be 427 patients per group with 90% power and one-sided alpha = 0.025. Non-inferiority testing was based on a non-inferiority margin of 0.050 L and SD of 0.225 L for trough FEV_1 (morning pre-dose FEV_1). Thus, rounding to 435 patients per group, the target sample size was 1,305 patients.

The two co-primary end points of all-cause deaths and time to first COPD exacerbation were evaluated using the Cox proportional hazards regression model. The trial was estimated to last approximately 3.5 years based on the expected mortality event rate. All patients were followed until study close-out; thus, the actual follow-up time for patients was between two and three years. The key secondary end

point defined within the SSS (trough FEV_1) was analyzed through week 120 using a restricted maximum likelihood–based repeated measures approach. Three hypotheses were tested in the following hierarchical order to preserve the type I error: 1) non-inferiority of Tio R 5 versus Tio H 18 on time to death, 2) non-inferiority of 2.5 mcg of tiotropium through the Respimat versus Tio H 18 on time to death, and 3) superiority of Tio R 5 versus Tio H 18 on time to first COPD exacerbation. Each test of the null hypothesis had to be rejected to proceed to the next test. The non-inferiority margin for the HR of time to death of 1.25 was determined based on practical considerations. If the upper bound of the 95% CI for the HR lies below 1.25, then non-inferiority was achieved. For the key secondary end point of trough FEV_1 in the SSS, the null and alternative hypotheses for non-inferiority apply with a non-inferiority margin of 0.050 L. If the lower bound of the 95% CI for the absolute difference in trough FEV_1 lay above –0.050 L, then non-inferiority was achieved. Non-inferiority tests were performed at the one-sided alpha = 0.025. Superiority tests were performed at the two-sided alpha = 0.05. A major goal of this trial was to obtain virtually complete follow-up of vital status. All patients lost to follow-up were treated as censored at the time of their last known vital status. For sub-study FEV_1 values that were missing due to worsening of COPD were imputed using worst observation carried forward.

a) Analysis Populations

In Study 205.249, there were 131 patients in the all randomized patients (ARP) population; however, two patients living together presumably interchanged their study medication and were excluded from all efficacy and safety analyses because the medication they used in each study period could not be verified. All other 129 patients were included in the full-analysis set (FAS). The FAS population consisted of all patients with data for at least one efficacy end point (baseline data and post-treatment data) for one period. Patients with data for only one treatment did not contribute to the comparison of treatments, but remained in the population. This was applied separately for each variable, meaning that the number of patients in the analysis could vary across variables and treatments. The FAS was the primary analysis set and was used for all efficacy analyses.

In these studies, three additional FAS subsets were defined:

- FAS – Primary End point (FAS-PEP), consisting of all patients contributing to the analysis of the primary end point; i.e., trough FEV_1 response
- FAS – Clinic Spirometry/Pulmonary Function Tests (FAS-PFT), consisting of all patients contributing to the analysis of at least one secondary end point derived from spirometric measurements
- FAS – Diary (FAS-DRY), consisting of all patients contributing to the analysis of at least one end point derived from patient diary card recordings.

The PP set consisted of all treatment periods of the FAS during which no relevant protocol deviations occurred and trough FEV_1 response was available after four weeks of treatment.

In studies 205.251 and 205.252, the primary efficacy analysis was conducted on the FAS, which consisted of all randomized patients with at least baseline data (pre-treatment at the end of the two-week run-in) and at least one adequate trough FEV_1 following at least five days of randomized treatment. There were no PP analyses in these studies. Additional FAS subsets were defined as follows:

- FAS-DRY population was defined as those patients included in the FAS who had baseline data and at least four days of diary data on treatment for at least one diary parameter.

In studies 205.254 and 205.255, the FAS consisted of all randomized patients with baseline data (pre-treatment observed on day 1) and data following at least five days on randomized treatment for at least

one primary end point. There were no PP analyses in these studies. In addition, the following subsets of the FAS were defined:

- FAS – clinic spirometry (FAS-PFT)
- FAS – SGRQ (FAS-QoL)
- FAS – Mahler TDI (FAS-TDI)
- FAS – diary (FAS-DRY) that included patients who had at least four diary observations in the run-in period and four diary observations on treatment
- FAS – COPD symptoms (FAS-SYM).

In Study 205.372, the following patient sets were defined:

- Randomized set (RAN), which comprised all randomized patients, whether treated or not.
- Treated set (TS), which included all patients who had been dispensed, and were documented to have taken, at least one dose of DB randomized treatment and had not been randomized to a specific site with questionable treatment assignment or administration. This set was used for the assessment of safety, concomitant medication, diagnoses, demographics, and other baseline characteristics.
- FAS, which included all patients who were dispensed and documented to have taken at least one dose of DB randomized treatment and had not been randomized to any of three sites with questionable data. This set was used for assessment of efficacy (e.g., COPD exacerbations).

In Study 205.452, the following analysis sets were defined:

- Death analysis set (DAS): This analysis set included all randomized patients, excluding only patients who had been documented as not treated.
- Treated set (TS): This analysis set included all randomized patients without data irregularities who had been documented to have taken at least one dose of investigational treatment.
- Spirometry sub-study (SSS): This analysis set included all patients in the TS who had signed informed consent to participate in the sub-study and who had at least baseline and one on-treatment trough FEV_1.

The DAS was used for the analyses of all mortality end points, and the TS was used in all other planned analyses in Study 205.452. The SSS was used in analyses of spirometry end points. No PP set was defined and no PP analysis was planned.

Across all studies (with the exception of 205.372), the safety populations or safety sets (SS) comprised all randomized patients with any available data.

3.3 Patient Disposition

Patient disposition and analyses populations for all eight trials are reported in Table 11. In studies 205.249 and 205.250, the disposition data include the Tio R 10 dose group, as only total study population results were reported. Overall, the proportion of patients who discontinued the trials ranged from approximately 5% to 34% across individual treatment groups. In general, the main reason for discontinuation appeared to be due to AEs, ranging from approximately 4% to 22% across treatment groups. In the trials that included Iprat 36 (205.251 and 205.252), discontinuations were markedly higher in the Iprat 36 (19.1% and 15.7%) groups compared with the Tio R 5 groups (9.1% and 8.7%), respectively, although discontinuations were also relatively high (16.7%) in the placebo group of Study 205.252. The highest discontinuations were reported in the placebo groups of studies 205.254 (28.5%) and 205.255 (34.1%) compared with the Tio R 5 groups (16.6% and 17.8%, respectively). In Study 205.372, discontinuations were similar between Tio R 5 (16.0%) and placebo (18.6%) and similarly in

Study 205.452 between Tio R 5 (22.9%) and Tio H 18 (22.6%) (Table 12). Vital status data were complete for 99.8% (Tio R 5) and 99.7% (Tio H 18) of patients in Study 205.452 (Table 13).

TABLE 11A: PATIENT DISPOSITION

Patient Disposition and Analyses Populations	Study							
	205.249	205.250	205.251			205.252		
			Tio R 5	Iprat 36	PL	Tio R 5	Iprat 36	PL
Screened, N	185	80	429			491		
Randomized, N	131	76	88	89	91	92	89	90
Completed, N (%)	93 (71.0)	72 (94.7)	80 (90.9)	72 (80.9)	84 (92.3)	84 (91.3)	75 (84.3)	75 (83.3)
Discontinued, N (%)	38 (29.0)	4 (5.3)	8 (9.1)	17 (19.1)	7 (7.7)	8 (8.7)	14 (15.7)	15 (16.7)
Primary Reason for Treatment Discontinuation, n (%)								
AEs	21 (16.0)	3 (3.9)	6 (6.8)	11 (12.4)	5 (5.5)	7 (7.6)	10 (11.2)	11 (12.2)
Administrative	17 (13.0)	1 (1.3)	2 (2.3)	5 (5.6)	2 (2.2)	0 (0)	3 (3.4)	2 (2.2)
Analysis Populations, N (%)								
ARP	131 (100)	76 (100)	88 (100)	89 (100)	91 (100)	92 (100)	89 (100)	90 (100)
Safety	129 (98.5)	76 (100)	88 (100)	89 (100)	91 (100)	92 (100)	89 (100)	90 (100)
PP	110 (84.0)	75 (98.7)	NA	NA	NA	NA	NA	NA
FAS or FAS-PEP	129 (98.5)	76 (100)	85 (97)	84 (94)	87 (96)	90 (98)	86 (97)	84 (93)
FAS-PFT	129 (98.5)	76 (100)	NA	NA	NA	NA	NA	NA
FAS-DRY	125 (95.4)	76 (100)	85 (97)	83 (93)	87 (96)	89 (97)	85 (96)	83 (92)

AE = adverse event; ARP = all randomized patients; FAS = full-analysis set; FAS-DRY = full-analysis set – diary; FAS-PEP = full-analysis set – primary end point; FAS-PFT = full-analysis set – clinic spirometry; Iprat 36 = ipratropium 36 mcg four times daily dose; NA = not applicable; PL = placebo; PP = per-protocol; Tio R 5 = Spiriva Respimat 5 mcg daily dose.
Note: In Study 205.249, two patients were excluded from all efficacy and safety analyses because it was unclear which treatment they had been given, as they lived together and interchanged medication. The only studies with PP analyses were 205.249 and 205.250. The ARP is considered to be equivalent to an intention-to-treat population.
Source: Clinical Study Report (CSR) 205.249,[1] CSR 205.250,[2] CSR 205.251,[3] and CSR 205.252.[12]

TABLE 11B: PATIENT DISPOSITION (CONTINUED)

Patient Disposition and Analyses Populations	Study					
	205.254		205.255		205.372	
	Tio R 5	PL	Tio R 5	PL	Tio R 5	PL
Screened, N	1,245		1,299		5,483	
Randomized, N	332	319	338	334	1,989	2,002
Completed, N (%)	277 (83.4)	228 (71.5)	278 (82.2)	220 (65.9)	1,671 (84.0)	1,629 (81.4)
Discontinued, N (%)	55 (16.6)	91 (28.5)	60 (17.8)	114 (34.1)	318 (16.0)	373 (18.6)
Primary Reason for Treatment Discontinuation, n (%)						
AEs	31 (9.3)	48 (15.0)	36 (10.7)	74 (22.2)	143 (7.2)	156 (7.8)
Administrative	18 (5.4)	34 (10.7)	18 (5.3)	34 (10.2)	89 (4.5)	98 (4.9)
Analysis Populations, N (%)						
ARP/RAN	332 (100)	319 (100)	338 (100)	334 (100)	1,989 (100)	2,002 (100)
Safety	332 (100)	319 (100)	338 (100)	334 (100)	1,952 (98.1)	1,965 (98.2)
PP	NA	NA	NA	NA	NA	NA
FAS or FAS-PEP	327 (98.5)	297 (93.1)	327 (96.7)	311 (93.1)	1,939 (97.5)	1,953 (97.6)
FAS-PFT	326 (98.2)	296 (92.8)	324 (95.9)	307 (91.9)	NA	NA
FAS-QoL	318 (95.8)	275 (86.2)	310 (91.7)	276 (82.6)	NA	NA
FAS-TDI	318 (95.8)	273 (85.6)	310 (91.7)	279 (83.5)	NA	NA

Patient Disposition and Analyses Populations	Study					
	205.254		205.255		205.372	
	Tio R 5	PL	Tio R 5	PL	Tio R 5	PL
FAS-SYM	326 (98.2)	295 (92.5)	325 (96.2)	304 (91.0)	NA	NA
FAS-DRY	324 (97.6)	295 (92.5)	322 (95.3)	311 (93.1)	NA	NA
TS	NA	NA	NA	NA	1,952 (98.1)	1,965 (98.2)

AE = adverse event; ARP = all randomized patients; FAS = full-analysis set; FAS-DRY = full-analysis set-diary; FAS-PEP = full-analysis set – primary end point; FAS-PFT = full-analysis set – clinic spirometry; FAS-QoL = full-analysis set – quality of life; FAS-SYM = full-analysis set – symptoms; FAS-TDI = full-analysis set – Transition Dyspnea Index; Iprat 36 = ipratropium 36 mcg four times daily dose; NA = not applicable; PL = placebo; PP = per-protocol; RAN = randomized set; Tio R 5 = Spiriva Respimat 5 mcg daily dose; TS = treated set.
Notes: In Study 205.372, due to questionable drug receipt and dispensing logs, 74 patients from site 91009 were excluded from the TS and Safety populations. Due to evidence of patients participating in another study (site 3314), 17 patients were excluded from the FAS. Due to questionable drug accountability data (site 1008), eight patients were excluded from the FAS. The ARP is considered to be equivalent to an intention-to-treat population.
Source: Clinical Study Report (CSR) 205.254,[4] CSR 205.255,[5] and CSR 205.372.[13]

TABLE 12: STUDY 205.452 (TIOSPIR) — PATIENT DISPOSITION

Patient Disposition and Analysis Populations	Treatment	
	Tio R 5 Tio	Tio H 18
Screened, N	20,313	
Entered/Randomized, N	5,729	5,713
Not treated, N	18	19
Eligible for vital status follow-up (DAS), N	5,711	5,694
Patients at sites with data irregularities/fraud, N	6	7
Treated, N (%)	5,705 (100.0)	5,687 (100.0)
Completed, N (%)	4,399 (77.1)	4,400 (77.4)
Discontinued, N (%)	1306 (22.9)	1,287 (22.6)
Reason for Treatment Discontinuation, n (%)		
AEs	606 (10.6)	635 (11.2)
Worsening of disease under study	171 (3.0)	185 (3.3)
Worsening of other disease	45 (0.8)	58 (1.0)
Other AE	390 (6.8)	392 (6.9)
Lack of efficacy	60 (1.1)	59 (1.0)
Non-compliant with protocol	66 (1.2)	41 (0.7)
Lost to follow-up	63 (1.1)	55 (1.0)
Patient refused to continue taking trial medication	335 (5.9)	319 (5.6)
Other	176 (3.1)	178 (3.1)
Analysis Populations, N (%)		
DAS	5,711 (99.7)	5,694 (99.7)
TS	5,705 (99.6)	5,687 (99.5)
SSS	461 (8.0)	445 (7.8)

AE = adverse event; DAS = death analysis set; SSS = spirometry sub-study; Tio R 5 = Spiriva Respimat 5 mcg daily dose; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; TS = treated set.
Source: Clinical Study Report 205.452.14.

TABLE 13: STUDY 205.452 (TIOSPIR) — OVERVIEW OF VITAL STATUS INFORMATION AT END OF THE OBSERVATION PERIOD (DAS)

Vital Status	Treatment n (%)

	Tio R 5	Tio H 18
Patients eligible for vital status follow-up (DAS)	5,711 (100.0)	5,694 (100.0)
Vital status complete	5,697 (99.8)	5,678 (99.7)
Alive	5,274 (92.3)	5,239 (92.0)
Died	423 (7.4)	439 (7.7)
Lost to follow-up	14 (0.2)	16 (0.3)

DAS = death analysis set; Tio R 5 = Spiriva Respimat 5 mcg daily dose; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose.

3.4 Exposure to Study Treatments

Median exposure to study drug was identical between treatment groups in all included studies, as summarized in Table 14. In Study 205.452, the median observation time from the start of treatment to the last known alive date was also almost identical between treatment groups (i.e., 870 days with Tio R 5 and 869 days with Tio H 18), as per Table 15.

TABLE 14: EXPOSURE TO STUDY TREATMENTS (DAYS)

Study and N	Duration (Days)		
	Mean (SD)	Median	Range
Study 205.249			
Tio R 5 (N = 112)	30.6 (4.8)	29.0	2 to 50
Tio H 18 (N = 112)	30.9 (5.7)	29.0	4 to 57
PL (N = 108)	28.3 (8.0)	29.0	2 to 48
Study 205.250			
Tio R 5 (N = 75)	29.7 (3.7)	29.0	3 to 34
Tio H 18 (N = 75)	30.2 (2.4)	29.0	25 to 39
PL (N = 76)	30.5 (3.6)	30.0	20 to 52
Study 205.251			
Tio R 5 (N = 88)	82.4 (17.5)	85.0	4 to 109
Iprat 36 (N = 89)	79.0 (23.7)	85.0	1 to 119
PL (N = 91)	81.8 (21.2)	85.0	1 to 131
Study 205.252			
Tio R 5 (N = 92)	83.0 (16.2)	85.0	10 to 120
Iprat 36 (N = 89)	79.1 (20.5)	85.0	1 to 100
PL (N = 90)	78.4 (23.3)	85.0	1 to 128
Study 205.254			
Tio R 5 (N = 332)	307.3 (84.3)	337.0	1 to 390
PL (N = 319)	272.3 (120.5)	337.0	1 to 409
Study 205.255			
Tio R 5 (N = 338)	302.2 (91.3)	337.0	2 to 412
PL (N = 334)	259.2 (126.2)	336.5	1 to 414
Study 205.372			
Tio R 5 (N = 1,952)	308.5 (85.9)	337.0	1 to 460
PL (N = 1,965)	299.5 (97.2)	337.0	1 to 455
Study 205.452 (TIOSPIR)			
Tio R 5 (N = 5,705)	726.2 (258.7)	835.0	1 to 1,022
Tio H 18 (N = 5,687)	728.1 (255.0)	835.0	1 to 1,023

Iprat 36 = ipratropium 36 mcg four times daily dose; PL = placebo; SD = standard deviation; Tio R 5 = Spiriva Respimat 5 mcg daily dose; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose.
Source: Clinical Study Report (CSR) 205.249,[1] CSR 205.250,[2] CSR 205.251,[3] CSR 205.252,[12] CSR 205.254,[4] CSR 205.255,[5] CSR 205.372,[13] and CSR 205.452.[14]

TABLE 15: STUDY 205.452 (TIOSPIR) — OBSERVATION TIME FROM TREATMENT START DATE TO LAST KNOWN ALIVE DATE, BY TREATMENT (DAS)

Treatment Group	Tio R 5	Tio H 18
DAS (N [%])	5,711 (100.0)	5,694 (100.0)
Observation time (days)		
Mean (SD)	840.1 (141.2)	837.1 (146.5)
Median	870.0	869.0
Range	18 to 1,081	9 to 1,094
Total observation time (years)	13,135.1	13,050.2
0 to 12 months (0 to 365 days)	137 (2.4)	152 (2.7)
12 to 18 months (366 to 547 days)	109 (1.9)	116 (2.0)
18 to 24 months (548 to 730 days)	342 (6.0)	378 (6.6)
24 to 30 months (731 to 912 days)	3,583 (62.7)	3,513 (61.7)
30 to 36 months (913 to 1,095 days)	1,540 (27.0)	1,535 (27.0)

DAS = death analysis set; SD = standard deviation; Tio R 5 = Spiriva Respimat 5 mcg daily dose; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose.
Source: Clinical Study Report 205.452.[14]

3.5 Critical Appraisal

3.5.1 Internal Validity

- In all included trials, the methods used for randomization (i.e., IVRS, IWRS, or computer-generated randomization lists) and methods of allocation concealment appeared to be appropriate. The double-dummy technique was used in the majority of trials, which is appropriate, especially since two distinct delivery devices (Respimat and HandiHaler) were used in the trials, making blinding difficult.
- Adequate sample sizes appear to have been determined in all studies based on a priori power calculations. Although the sample sizes were small in studies 205.249 (N = 76) and 205.250 (N = 131) compared with the other trials, these trials appeared to be adequately powered to demonstrate non-inferiority, and a pooled analysis of the trials was pre-specified in the protocols.
- Studies 205.249, 205.250, and TIOSPIR evaluated the non-inferiority of Tio R 5 and Tio H 18, whereas studies 205.251 and 205.252 evaluated the non-inferiority of Tio R 5 and Iprat 36, all based on trough FEV_1 response. It was stated in these studies that the non-inferiority margin for trough FEV_1 response was 0.05 L. As described in Appendix 5: Validity of Outcomes, the MCID for trough FEV_1 response is generally considered to be between 0.10 L and 0.14 L. According to the manufacturer, the choice of 0.05 L was based on the expectation that about two-thirds of the FEV_1 response of 0.150 L (i.e., expected for active bronchodilators compared with placebo in patients with moderate-to-severe COPD) would be maintained in an active control comparison. TIOSPIR also evaluated the non-inferiority between Tio R 5 and Tio H 18 with respect to time to death based on the upper bound of the 95% CI for the HR lying below 1.25. No clear reason or description as to methods used to derive this non-inferiority margin was provided. In addition, the only trials to include a PP analysis to confirm the non-inferiority hypotheses were studies 205.249 and 205.250. In general, the results of a PP analysis are preferred as the primary analysis population for non-inferiority inferences, with confirmation of results in the intention-to-treat population. Non-inferiority may be claimed if the non-inferiority margin is not exceeded in both populations.
- In studies that tested more than one null hypothesis (i.e., superiority and non-inferiority as in studies 205.249, 205.250, 205.251, and 205.252, or multiple co-primary end points such as in studies 205.254 and 205.255, statistical comparisons were appropriately tested in a stepwise manner. Each step was considered confirmatory only if all previous steps were successful. However, it was not clear whether methods were used to adjust for multiplicity for secondary outcome analyses.

- Across all trials, efficacy analyses were conducted on the FAS population or subsets of the FAS (as defined by the manufacturer). In general, the FAS included all treated patients who had baseline data and post-treatment data. This is not a true ITT population, but rather a modified ITT population. The majority of FAS populations and FAS subsets across trials included ≥ 92% of all randomized patients, with the exception of the FAS-QoL (86.2%) and FAS-TDI (85.6%) subsets in Study 205.252 and the FAS-TDI (83.5%) subset in Study 205.255. Hence, aside from the aforementioned exceptions, use of the FAS instead of a true ITT population for the primary analysis is unlikely to affect the validity of the outcomes.
- The proportion of patients who discontinued the trials ranged from approximately 5% to 34% across individual treatment groups in the included trials. The highest discontinuations were reported in the placebo groups of studies 205.254 (28.5%) and 205.255 (34.1%). There is potential for attrition bias and compromised randomization with high withdrawal and dropout rates in clinical trials.
- There was very limited information from the clinical trial data on patient satisfaction with the Respimat inhaler compared with the HandiHaler devices. The only data available appear to be the results of a patient satisfaction questionnaire administered to a subset of patients participating in Study 205.252 at US sites. Patients were trained in the proper use of the inhaler devices in the trials and study personnel observed patients inhaling medication during study visits; however, there are no data available on the proportions of patients who used the various devices correctly or incorrectly. This has implications for the evaluation of patient satisfaction and inhaler preference, as while patients may have found a particular inhaler device easier to use than, or preferable to, another, it could be that the patients were not using the devices correctly.
- Overall, the outcomes reported in the trials (i.e., trough FEV_1 response, SGRQ, TDI, symptoms) are consistent with other trials of COPD pharmacotherapies; however, only four trials (205.254, 205.255, 205.372, and 205.452) included COPD exacerbations as either a co-primary end point or a secondary end point. Furthermore, the severity of COPD exacerbations was reported only in studies 205.372 and 205.452. More data on COPD exacerbation rates (particularly severe exacerbations) would have been useful, as COPD exacerbations are an important outcome for management decisions in COPD and health care resource use.[16]
- No data were available for some outcomes identified in the protocol such as overall health care utilization, exercise tolerance, or days of missed work or school.
- Treatment compliance appears to have been based upon self-reported use of study medication by patients (i.e., recorded on diary cards). It is possible that this method could have introduced reporting bias; however, patients were required to return all used and unused devices for confirmation of use by study personnel. There is also uncertainty about how compliance rates observed in a controlled clinical trial setting will translate into real-world use.

3.5.2 External Validity

- Various baseline patient characteristics may affect the generalizability of the results of the included trials to Canadian COPD patients. There appeared to be underrepresentation of female patients, as more than 50% of all patients across the trials were male, ranging from 57% to 83% in individual treatment groups. Almost all included patients were Caucasian (> 90%) with the exception of studies 205.372 and 205.452, in which roughly 68% and 81% of patients, respectively, were Caucasian. One-third or more of all patients (approximately 30% to 47%) were also current smokers.
- In all studies, with the exception of Study 205.372 and 205.452, patients who had previously received tiotropium through a clinical trial or who had received the commercially available formulation were excluded. While this was done to protect against selection bias, these studies do not reflect the majority of patients who would have been candidates for Tio R 5, as it is expected a

large proportion of patients who are currently using Spiriva HandiHaler will likely be transitioned to Spiriva Respimat.

- The exclusion from the trials of patients with unstable cardiac conditions is of concern, especially given the comorbid association of cardiac disease and COPD. The clinical expert involved in the review noted that this is usual practice in clinical trials and that clinicians may be hesitant to initiate LAMA therapy in the presence of unstable cardiac conditions.
- The comparators in the clinical trials were appropriate, especially since the key comparison of interest is between tiotropium inhalation solution administered by the Respimat inhaler versus tiotropium dry powder for inhalation administered by the HandiHaler device, which was directly compared head-to-head in three trials (205.249, 205.250, and 205.452). Outcome measures were also appropriate and in keeping with outcomes typically measured in trials of pharmacotherapy for COPD (e.g., spirometry, SGRQ, TDI, symptoms); the MCID for these outcomes were either met or exceeded in the included trials.
- In studies 205.251 and 205.252, Iprat 36 failed to demonstrate superiority (based on trough FEV_1 response) when compared with placebo. In Study 205.252, the treatment difference between Tio R 5 and Iprat 36 exceeded the non-inferiority margin and the comparison was statistically significant in favour of Tio R 5. Discontinuation rates from the Iprat 36 groups in these trials were higher than other treatment groups, ranging from 15.7% to 19.1%. Altogether, these findings suggest that the dose of ipratropium may not have been optimal. According to the clinical expert consulted for this review, the indicated dose of ipratropium (36 mcg four times daily) may not be an optimal dose, as in clinical practice ipratropium doses of twice this magnitude (i.e., four actuations or 72 mcg four times a day) have been used. Therefore, if higher doses of ipratropium are used in clinical practice, the dose used in the trials may compromise the generalizability of the findings of studies 205.251 and 205.252 to Canadian COPD patients.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 4). See Appendix 4 for detailed efficacy data.

3.6.1 Mortality

Very few deaths were reported in the trials of shorter duration (i.e., two deaths each in studies 205.249 [1.5%] and 205.250 [2.6%] over 28 weeks), no deaths in Study 205.251, and one death each in the Tio R 5 [1.1%] and Iprat 36 [1.1%] groups of Study 205.252 over 12 weeks (Table 27). As expected, the number of deaths were higher in the longer trials (i.e., seven deaths [2.1%] in the Tio R 5 group and five deaths [1.6%] in the placebo group of Study 205.254, and five deaths [1.5%] in the Tio R 5 group and no deaths in the placebo group of Study 205.255 over one year (Table 28).

In Study 205.372, there were 52 deaths (2.7%) in the Tio R 5 group and 38 deaths (1.9%) in the placebo group over one year (Table 29). Although there were more deaths in the Tio R 5 group, an analysis of fatal events revealed a non-statistically significant rate ratio of all fatal events of 1.38 (95% CI, 0.91 to 2.10); *P* = 0.1297 (Table 29). The rate ratio of fatal events was also not statistically significant when causes of death by individual system organ classes were examined. The rate ratios of fatal events due to cardiac disorders (2.27 [95% CI, 0.70 to 7.37]; *P* = 0.1724), lower respiratory system disorders (0.57 [95% CI, 0.25 to 1.28]; *P* = 0.1739), or other respiratory system disorders (2.52 [95% CI, 0.49 to 13.01]; *P* = 0.2686) were not statistically significant.

In TIOSPIR, there were 423 deaths (7.4%) in the Tio R 5 group and 439 deaths (7.7%) in the Tio H 18 group over three years (DAS, including vital status follow-up), as per Tables 30 and 31. The corresponding

HR was 0.957 (95% CI, 0.837 to 1.094). The upper limit of the 95% CI for the HR comparison of Tio R 5 and Tio R 18 was below the pre-specified non-inferiority margin of 1.25; thus, the primary comparison between the treatments for death from any cause was shown to be non-inferior in the DAS population. The rate ratio for all deaths was also not statistically significant (i.e., 0.96 [95% CI, 0.84 to 1.09]). An analysis of the causes of death by system organ class did not reveal any statistically significant differences between treatments for any classification, as per Table 33.

3.6.2 Chronic Obstructive Pulmonary Disease Exacerbations

COPD exacerbations were only included as an outcome in four studies: 205.254, 205.255, 205.372, and 205.452. In studies 205.254 and 205.255, COPD exacerbations were one of four co-primary end points, whereas in Study 205.372 and 205.452, time to first COPD exacerbation was a co-primary end point and numbers of exacerbations, patients with exacerbations, or patients with hospitalizations for exacerbations were secondary end points. The results for COPD exacerbations were only available from a pooled analysis for studies 205.254 and 205.255, and results by exacerbation severity were only reported in studies 205.372 and 205.452.

For the pooled analysis of COPD exacerbations in studies 205.254 and 205.255, there were 249 out of 670 patients (37.2%) in the Tio R 5 group compared with 288 out of 653 patients (44.1%) in the placebo group that experienced one or more COPD exacerbations (Table 34). The odds ratio (OR) for experiencing an exacerbation was 0.75 (95% CI, 0.60 to 0.93; $P < 0.01$), favouring Tio R 5. Time to first exacerbation was also statistically significantly shorter in the placebo group (86 days) compared with the Tio R 5 group (160 days) ($P < 0.001$). The probability of remaining exacerbation-free was statistically significantly greater with Tio R 5 when compared with placebo. There were 39 patients (5.8%) in the Tio R 5 group compared with 44 patients (6.7%) in the placebo group who had one or more hospitalizations due to COPD exacerbations.

In Study 205.372, the majority of COPD exacerbations in both the Tio R 5 and placebo groups were of moderate-to-severe severity (Table 36). Of the total number of exacerbations experienced by patients, approximately 75% of exacerbations in each group required antibiotic treatment, and approximately 50% of exacerbations in each group required treatment with oral or intravenous steroids (Table 35). There were 685 patients (35.3%) in the Tio R 5 group and 842 patients (43.1%) in the placebo group who experienced one or more exacerbations, corresponding with a HR for time to first COPD exacerbation of 0.693 (95% CI, 0.625 to 0.769; $P < 0.0001$), favouring Tio R 5. The proportion of patients with one or more moderate-to-severe exacerbations was greater in the placebo group (34.1%) compared with the Tio R 5 group (27.7%), corresponding with a HR of 0.699 (95% CI, 0.622 to 0.786; $P < 0.0001$). There were also fewer patients with one or more hospitalizations due to exacerbations in the Tio R 5 group (8.3%) compared with the placebo group (10.1%); (HR = 0.728 [95% CI, 0.589 to 0.901; $P = 0.0034$]).
In TIOSPIR, similar proportions of patients in the Tio R 5 group (47.9%) and the Tio H 18 group (48.9%) had COPD exacerbations, corresponding with a HR of 0.978 (95% CI, 0.928 to 1.032; $P = 0.4194$) (Table 39). The proportions of patients who had moderate-to-severe COPD exacerbations were also similar between treatment groups: Tio R 5 (47.2%) and Tio H 18 (48.0%); (HR = 0.983 [95% CI, 0.932 to 1.037; $P = 0.5377$]) (Table 40). In addition, the proportions of patients with hospitalizations due to COPD exacerbations were very similar between Tio R 5 (14.5 %) and Tio H 18 (14.3%), corresponding with a HR of 1.024 (95% CI, 0.929 to 1.128; $P = 0.6384$) (Table 42).

3.6.3 Quality of Life

Change in QoL, as measured by the SGRQ, was one of four co-primary end points in studies 205.254 and 205.255 and a secondary end point in Study 205.372 (Table 44). In studies 205.254 and 205.255,

statistically significant treatment differences in favour of Tio R 5 in SGRQ total and domain scores from baseline to day 337 were observed in both studies. Statistically significant differences between Tio R 5 and placebo were observed for the domain scores of symptoms and impacts and the total SGRQ scores in both trials. No statistically significant treatment differences were observed in the domain score of activities in either trial. In Study 205.372, statistically significant treatment differences in all SGRQ domain scores (symptoms, activities, and impacts) and total scores were found when Tio R 5 and placebo were compared on day 337 ($P < 0.0001$ for all).

A difference of ≥ 4 points in the SGRQ total score versus placebo at study end, or a ≥ 4 points from baseline is considered to be the MCID for this measure.[40] At day 337, the magnitude of the treatment difference in SGRQ total scores between Tio R 5 and placebo was –3.269 (95% CI, –5.224 to –1.315) in Study 205.254, –3.713 (95% CI, –5.778 to –1.647) in Study 205.255, and –2.9 (95% CI, –3.9 to –2.0) in Study 205.372. Thus, the differences between Tio R 5 and placebo in the SGRQ total score did not reach the MCID in any of the three trials where QoL was measured.

3.6.4 Pulmonary Function

Trough FEV_1 response (i.e., the change from baseline to end of treatment in trough FEV_1) was the primary efficacy outcome in studies 205.249, 205.250, 205.251, and 205.252, one of the four co-primary end points in studies 205.254 and 205.255, and one of two co-primary end points in Study 205.372. In Study 205.452, trough FEV_1 was defined as a key secondary end point within the SSS set. The generally accepted MCID in FEV_1 is between 0.10 L and 0.14 L.[41]

In studies 205.249 and 205.250, treatment differences in trough FEV_1 response at day 29 (end of each four-week treatment period) were statistically significant for the tests of superiority of Tio R 5 and Tio H 18 each with placebo, respectively, in both trials (Table 45). In addition, based on the manufacturer's pre-specified non-inferiority margin of 0.05 L, non-inferiority of Tio R 5 with Tio H 18 was demonstrated in both trials as the lower CI bound for the mean treatment differences in trough FEV_1 response did not exceed –0.05 L (i.e., lower CI bound was 0.013 [$P < 0.001$] for non-inferiority in Study 205.249 and lower CI bound was –0.039 [$P = 0.006$] for non-inferiority in Study 205.250). The magnitude of the treatment differences in trough FEV_1 response did exceed the MCID of 0.100 L for Tio R 5 versus placebo in both studies (i.e., 0.116 L in Study 205.249 and 0.126 L in Study 205.250) and for Tio H 18 versus placebo in Study 205.250 (0.125 L), but the MCID was not met in Study 205.249 (0.070 L). The PP analyses confirmed the non-inferiority findings for the FAS.

In studies 205.251 and 205.252, treatment differences in trough FEV1 response at day 85 (end of the 12-week treatment period) were statistically significant in favour of Tio R 5 compared with placebo for the superiority comparison in both studies (Table 46). The magnitude of the treatment differences in trough FEV1 response also exceeded the MCID when Tio R 5 was compared with placebo in both studies (i.e., 0.109 L in Study 205.251 and 0.124 L in Study 205.252). In contrast, in both studies treatment differences between Iprat 36 and placebo did not reach statistical significance, and the treatment differences (i.e., 0.060 L in Study 205.249 and 0.044 L in Study 205.250) between Iprat 36 and placebo did not exceed the MCID for trough FEV1 response (Table 46). Non-inferiority of Tio R 5 with Iprat 36 was demonstrated in both trials based on the pre-specified, non-inferiority margin of 0.05 L (i.e., the lower 95% CI bound was –0.024 [$P < 0.0041$] for non-inferiority in Study 205.251, and the lower 95% CI bound was 0.024 [$P < 0.001$] for non-inferiority in Study 205.252). In addition, Tio R 5 demonstrated superiority versus Iprat 36 (two-sided $P = 0.005$ for superiority) in Study 205.252, but not in Study 205.251 (two-sided $P = 0.1897$ for superiority).

In studies 205.254, 205.255, and 205.372, the treatment differences between Tio R 5 and placebo in trough FEV_1 response at day 337 (end of the 48-week treatment period) were statistically significant ($P < 0.0001$) in all three trials (Table 47). The magnitude of the treatment differences between Tio R 5 and placebo were 0.142 L in Study 205.254, 0.113 L in Study 205.255, and 0.102 L in Study 205.372, all exceeding the MCID.

In TIOSPIR, the comparison of trough FEV_1 response through 120 weeks in the subset of patients in the SSS set demonstrated that Tio R 5 (n = 461) and Tio H 18 (n = 445) were non-inferior, as the adjusted mean treatment difference was –0.010 L (95% CI: –0.038 to 0.018), as detailed in Table 48.

3.6.5 Chronic Obstructive Pulmonary Disease Symptoms

COPD symptom scores were included as an outcome in studies 205.251, 205.252, 205.254, and 205.255. In studies 205.251 and 205.252, COPD symptoms scores (i.e., wheezing, shortness of breath, coughing, and tightness of chest) were a secondary end point. In studies 205.254 and 205.255, the Mahler TDI focal score was one of the four co-primary efficacy end points and COPD symptoms scores were a secondary end point. It is generally agreed that a one-unit change in the TDI focal score represents the MCID.[42]

In Study 205.251, statistically significant treatment differences at day 85 (end of the 12-week treatment) were found only for the symptom of tightness of chest for the comparison of Tio R 5 versus placebo and for shortness of breath and tightness of chest for the comparison of Tio R 5 versus Iprat 36 (Table 49). In Study 205.251, statistically significant treatment differences were found for the symptom of wheezing for the comparison of Tio R 5 versus placebo and coughing for the comparison of Iprat 36 versus placebo. All other comparisons of treatment differences in COPD symptom scores did not reach statistical significance in either study.

In Study 205.254 and 205.255, statistically significant treatment differences at day 337 (end of 48-week treatment) were found for all comparisons of Tio R 5 versus placebo for all symptom scores (wheezing, shortness of breath, coughing, and tightness of chest) in both studies (Table 50). Treatment differences in Mahler TDI focal scores were also statistically significantly different between Tio R 5 and placebo, and the treatment differences exceeded the MCID in both studies (i.e., 1.104 in Study 205.254 and 1.011 in Study 205.255) as per Table 51.

No data were available from the included studies for the key outcomes of health care resource utilization or exercise tolerance.

3.6.6 Other Efficacy Outcomes

a) Rescue Medication Use

Use of rescue medication (i.e., salbutamol MDI) was reported as a study outcome in studies 205.249, 205.250, 205.251, 205.252, 205.254, and 205.255. In studies 205.249 and 205.250, daily use of daytime, nighttime or 24-hour rescue medication use over the four-week treatment periods appeared to be very similar between Tio R 5 and Tio H 18, and numerically higher with placebo treatment, as shown in Table 52. No statistical comparisons between treatment groups were conducted.

In studies 205.251 and 205.252, at week 12 the only statistically significant treatment difference in weekly mean number of occasions of rescue medication use was for the comparison of Tio R 5 versus placebo in Study 205.252 (Table 53). All other comparisons of treatment differences in both studies were not statistically significantly different.

In studies 205.254 and 205.255, at week 48 the weekly mean number of occasions of rescue medication use was statistically significantly less with Tio R 5 compared with placebo in both trials (Table 54).

b) Patient Adherence and Satisfaction

Patient compliance or adherence to study medication was high across all included studies (Table 55 to Table 59). No statistical comparisons were conducted between treatment groups in the included trials; however, compliance measured as medication taken (% prescribed), was high (> 95%) with all devices (Respimat, HandiHaler, or MDI).

In Study 205.252, a patient satisfaction questionnaire was administered at US study sites (Table 60). Overall, there was a high degree of satisfaction with both the Respimat inhaler and the MDI. Statistical comparisons were conducted in patients who rated both devices, and although satisfaction was similar for the two devices in most cases, there was a statistically significant difference in favour of the Respimat device in the ability to tell the amount of medication left in the container, inhaler durability, environmentally friendly nature of the inhaler, and higher satisfaction with the MDI in the overall convenience of carrying the inhaler. The proportions of patients having a problem were low for both devices.

No data from the included studies were available for days of missed work or school.

3.7 Harms

Only those harms identified in the review protocol (Table 4) are reported below.

3.7.1 Adverse Events

Treatment-emergent AEs for all included trials are summarized in Table 16 through Table 19. In studies 205.249 and 205.250 (four-week treatment periods; 28 weeks total duration), the proportions of patients with AEs ranged from 28.6% to 54.7% (Tio R 5), 27.7% to 44.0% (Tio H 18), and 33.3% to 72.4% (placebo) as detailed in Table 16. The most frequently reported AEs (by preferred term) were COPD exacerbations in Study 205.249 (approximately 7% per group) and in Study 205.250 (13.3% to 21.1% across the three treatment groups). In Study 205.250, nasopharyngitis (13.3% to 18.4%) and exacerbated dyspnea (9.3% to 25.0%) were the next most frequent AEs across the three treatment groups. The highest frequency of AEs occurred in the placebo groups of both trials (33.3% and 72.4%, respectively).

TABLE 16: HARMS — STUDIES 205.249 AND 205.250 OVER FOUR-WEEK TREATMENT PERIODS (SAFETY SET)

Harm	Study, n (%)					
	205.249			205.250		
	Tio R 5 N = 112	Tio H 18 N = 112	PL N = 108	Tio R 5 N = 75	Tio H 18 N = 75	PL N = 76
AEs						
Patients with ≥ 1 AE	32 (28.6)	31 (27.7)	36 (33.3)	41 (54.7)	33 (44.0)	55 (72.4)
Most Frequent AEs (by PT)[a]						
Upper respiratory tract infections	5 (4.5)	2 (1.8)	2 (1.9)	-	-	-
Chronic obstructive airways disease — exacerbated	8 (7.1)	8 (7.1)	8 (7.4)	10 (13.3)	13 (17.3)	16 (21.1)
Influenza	-	-	-	0 (0)	2 (2.7)	3 (3.9)
Nasopharyngitis	-	-	-	13 (17.3)	10 (13.3)	14 (18.4)
Dyspnea — exacerbated	-	-	-	10 (13.3)	7 (9.3)	19 (25.0)
SAEs						
Patients with ≥ 1 SAE	5 (4.5)	4 (3.6)	5 (4.6)	2 (2.7)	1 (1.3)	2 (2.6)
Most Frequent SAEs (by PT)[b]						
Chronic obstructive airways disease — exacerbated	2 (1.8)	1 (0.9)	2 (1.9)	1 (1.3)	1 (1.3)	2 (2.6)
WDAEs						
Patients with AEs leading to withdrawal	3 (2.7)	4 (3.6)	12 (11.1)	1 (1.3)	0 (0)	2 (2.6)
Most Common Reasons for Withdrawal (by PT)[b]						
Chronic obstructive airways disease — exacerbated	1 (0.9)	1 (0.9)	3 (2.8)	-	-	-
Dyspnea	0 (0)	1 (0.9)	2 (1.9)	-	-	-
Dyspnea — exacerbated	0 (0)	0 (0)	2 (1.9)	-	-	-

AE = adverse event; PL = placebo; PT = preferred term; SAE = serious adverse event; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; Tio R 5 = Spiriva Respimat 5 mcg daily dose; WDAE = withdrawal due to adverse event.

[a] Most frequent AEs were those reported by > 3% of patients in at least one of the treatment periods. (Note that the 3% may be in the Tio R 10 group, which is not included in these data.)

[b] Most frequent SAEs and WDAEs were those reported in > n = 1 patient in at least one treatment period.

Note: "-" means not reported by > 3% (AEs) or in > n = 1 patient (SAEs and WDAEs) in at least one treatment period.

Source: Clinical Study Reports 205.249[1] and 205.250.[2]

In studies 205.251 and 205.252 (12 weeks' duration), the proportions of patients with AEs ranged from 47.7% to 57.6% (Tio R 5), 55.1% to 64.0% (Iprat 36), and 49.5% to 68.9% (placebo) as detailed in Table 17. Similar to the previous trials, the most frequently reported AEs (by preferred term) were COPD exacerbations in Study 205.251 (8.8% to 13.5%) and Study 205.252 (8.7% to 14.4%) across the three treatment groups. The proportions of patients with COPD exacerbation AEs in the Tio R 5 groups were 8.7% and 10.2%, respectively, 13.5% with Iprat 36 (both trials), and 8.8% and 14.4%, respectively, with placebo. The proportions of patients with dry mouth were highest in the Tio R 5 groups (4.5% and 12.0%, respectively) compared with Iprat 36 (2.3% and 5.6%, respectively), and placebo (2.2% for both) in the two trials. The proportion of patients with pneumonia (> 3%) was reported only in Study 205.251 (i.e., 3.4% with Iprat 36 compared with 2.2% with placebo, and no cases with Tio R 5). In Study 205.252, 3.4% of patients in the Iprat 36 group, and no patients in the Tio R 5 or placebo groups, had an AE of atrial fibrillation.

TABLE 17: HARMS — STUDIES 205.251 AND 205.252 OVER 12-WEEK TREATMENT PERIODS (SAFETY SET)

Harm	Study, n (%)					
	205.251			205.252		
	Tio R 5 N = 88	Iprat 36 N = 89	PL N = 91	Tio R 5 N = 92	Iprat 36 N = 89	PL N = 90
AEs						
Patients with ≥ 1 AE, N (%)	42 (47.7)	49 (55.1)	45 (49.5)	53 (57.6)	57 (64.0)	62 (68.9)
Most Frequent AEs (by PT)[a]						
Diarrhea	2 (2.3)	2 (2.2)	1 (1.1)	1 (1.1)	4 (4.5)	3 (3.3)
Mouth dry	4 (4.5)	2 (2.3)	2 (2.2)	11 (12.0)	5 (5.6)	2 (2.2)
Nausea	0 (0)	3 (3.4)	0 (0)	0 (0)	3 (3.4)	3 (3.3)
Urinary tract infection	2 (2.3)	0 (0)	3 (3.3)	7 (7.6)	3 (3.4)	1 (1.1)
Headache	2 (2.3)	4 (4.5)	7 (7.7)	4 (4.3)	3 (3.4)	6 (6.7)
Bronchitis	4 (4.5)	3 (3.4)	1 (1.1)	4 (4.3)	5 (5.6)	6 (6.7)
COPD exacerbation	9 (10.2)	12 (13.5)	8 (8.8)	8 (8.7)	12 (13.5)	13 (14.4)
Cough	3 (3.4)	5 (5.6)	2 (2.2)	4 (4.3)	5 (5.6)	4 (4.4)
Dyspnea	2 (2.3)	5 (5.6)	2 (2.2)	2 (2.2)	4 (4.5)	7 (7.8)
Pneumonia	0 (0)	3 (3.4)	2 (2.2)	-	-	-
Influenza	0 (0)	1 (1.1)	3 (3.3)	-	-	-
Pharyngitis	7 (8.0)	8 (9.0)	12 (13.2)	4 (4.3)	7 (7.9)	8 (8.9)
Pharyngolaryngeal pain	2 (2.3)	1 (1.1)	1 (1.1)	3 (3.3)	3 (3.4)	5 (5.6)
Atrial fibrillation	-	-	-	0 (0)	3 (3.4)	0 (0)
Abdominal pain	-	-	-	1 (1.1)	3 (3.4)	1 (1.1)
Vomiting	-	-	-	1 (1.1)	1 (1.1)	3 (3.3)
Chest pain	-	-	-	4 (4.3)	0 (0)	2 (2.2)
Edema	-	-	-	1 (1.1)	1 (1.1)	3 (3.3)
Back pain	-	-	-	1 (1.1)	5 (5.6)	7 (7.8)
Neck pain	-	-	-	3 (3.3)	1 (1.1)	0 (0)
Dizziness	-	-	-	3 (3.3)	3 (3.4)	1 (1.1)
Insomnia	-	-	-	1 (1.1)	1 (1.1)	0 (0)
Hoarseness	-	-	-	4 (4.3)	1 (1.1)	0 (0)
Nasal congestion	-	-	-	0 (0)	3 (3.4)	0 (0)
Sinusitis	-	-	-	5 (5.4)	1 (1.1)	2 (2.2)
Upper respiratory tract infection	-	-	-	4 (4.3)	1 (1.1)	5 (5.6)
Pruritus	-	-	-	0 (0)	0 (0)	0 (0)
SAEs						
Patients with ≥ 1 SAE	2 (2.3)	8 (9.0)	4 (4.4)	2 (2.2)	9 (10.1)	1 (1.1)
Most Frequent SAEs (by PT)[b]						
COPD exacerbation	0 (0)	2 (2.2)	0 (0)	-	-	-
Pneumonia	0 (0)	3 (3.4)	0 (0)	-	-	-
Atrial fibrillation	-	-	-	0 (0)	2 (2.2)	0 (0)
Pulmonary edema	-	-	-	0 (0)	2 (2.2)	0 (0)
WDAEs						
Patients with AEs leading to withdrawal	6 (6.8)	11 (12.4)	5 (5.5)	7 (7.6)	9 (10.1)	11 (12.2)
Most Common Reasons for Withdrawal (by PT)[b]						
COPD exacerbation	2 (2.3)	8 (9.0)	2 (2.2)	3 (3.3)	1 (1.1)	5 (5.6)
Dyspnea	1 (1.1)	0 (0)	2 (2.2)	0 (0)	1 (1.1)	2 (2.2)
Pneumonia	0 (0)	2 (2.2)	0 (0)			
Atrial fibrillation	-	-	-	0 (0)	2 (2.2)	0 (0)

Harm	Study, n (%)					
	205.251			205.252		
	Tio R 5 N = 88	Iprat 36 N = 89	PL N = 91	Tio R 5 N = 92	Iprat 36 N = 89	PL N = 90
Back pain	-	-	-	0 (0)	0 (0)	2 (2.2)
Pulmonary edema	-	-	-	0 (0)	2 (2.2)	0 (0)

AE = adverse event; COPD = chronic obstructive pulmonary disease; Iprat 36 = ipratropium 36 mcg four times daily dose; PL = placebo; PT = preferred term; SAE = serious adverse event; Tio R 5 = Spiriva Respimat 5 mcg daily dose; WDAE = withdrawal due to AEs.

[a] Most frequent AEs were those reported by > 3% of patients in at least one of the treatment periods. (Note that the 3% may be in the Tio R 10 group which is not included in these data.)

[b] Most frequent SAEs and WDAEs were those reported in > n = 1 patient in at least one treatment period.

Note: "-" means not reported by > 3% (AEs) or in > n = 1 patient (SAEs and WDAEs) in at least one treatment period.

Source: Clinical Study Reports 205.251[3] and 205.252.[12]

In studies 205.254, 205.255, and 205.372 (one year's duration), the proportions of patients with AEs ranged from 70.1% to 78.4% with Tio R 5 and 69.3% to 79.6% with placebo as detailed in Table 18. As with previous trials, the most frequently reported AEs (by preferred term) were COPD exacerbations in Study 205.254 (31.6% to 39.5%), Study 205.255 (32.8% to 44.6%) and Study 205.372 (32.8% to 38.6%) across the two treatment groups. The proportions of patients with COPD exacerbations in the Tio R 5 groups ranged from 31.6% to 34.0%, and from 38.6% to 44.6% with placebo. The proportions of patients with dry mouth were also highest in the Tio R 5 groups (3.1% to 8.9%) compared with placebo (1.3% to 3.0%) across the three trials. The proportion of patients with pneumonia (> 3%) ranged from 3.0% to 3.6% with Tio R 5, and 1.3% to 3.8% with placebo. The proportions of patients with nasopharyngitis ranged from 8.0% to 15.7% in the Tio R 5 groups compared with 7.2% to 9.4% in the placebo groups.

TABLE 18: HARMS — STUDIES 205.254, 205.255, AND 205.372 OVER 48-WEEK TREATMENT PERIODS (SAFETY SET)

Harm	Study, n (%)					
	205.254		205.255		205.372	
	Tio R 5 N = 332	PL N = 319	Tio R 5 N = 338	PL N = 334	Tio R 5 N = 1,952	PL N = 1,965
AEs						
Patients with ≥ 1 AE	240 (72.3)	236 (74.0)	265 (78.4)	266 (79.6)	1,369 (70.1)	1,361 (69.3)
Most Frequent AEs (by PT)[a]						
Diarrhea	-	-	6 (1.8)	12 (3.6)	-	-
Mouth dry	18 (5.4)	4 (1.3)	30 (8.9)	10 (3.0)	60 (3.1)	27 (1.4)
Urinary tract infection	4 (1.2)	2 (0.6)	13 (3.8)	5 (1.5)	-	-
Headache	12 (3.6)	9 (2.8)	19 (5.6)	15 (4.5)	-	-
Bronchitis	13 (3.9)	11 (3.4)	16 (4.7)	16 (4.8)	67 (3.4)	95 (4.8)
COPD exacerbation	105 (31.6)	126 (39.5)	115 (34.0)	149 (44.6)	641 (32.8)	759 (38.6)
Cough	14 (4.2)	16 (5.0)	19 (5.6)	11 (3.3)	124 (6.4)	108 (5.5)
Dyspnea	23 (6.9)	23 (7.2)	18 (5.3)	28 (8.4)	136 (7.0)	152 (7.7)
Pneumonia	10 (3.0)	4 (1.3)	12 (3.6)	7 (2.1)	65 (3.3)	74 (3.8)
Influenza	13 (3.9)	13 (4.1)	14 (4.1)	17 (5.1)	-	-
Pharyngolaryngeal pain	11 (3.3)	4 (1.3)	-	-	-	-
Abdominal pain	11 (3.3)	6 (1.9)	13 (3.8)	7 (2.1)	-	-
Chest pain	-	-	13 (3.8)	7 (2.1)	-	-
Edema	-	-	15 (4.4)	9 (2.7)	-	-
Back pain	18 (5.4)	15 (4.7)	12 (3.6)	7 (2.1)	-	-

Harm	Study, n (%)					
	205.254		205.255		205.372	
	Tio R 5 N = 332	PL N = 319	Tio R 5 N = 338	PL N = 334	Tio R 5 N = 1,952	PL N = 1,965
Upper respiratory tract infection	26 (7.8)	24 (7.5)	27 (8.0)	28 (8.4)	124 (6.4)	144 (7.3)
Lower respiratory tract infection	15 (4.5)	13 (4.1)	-	-	-	-
Nasopharyngitis	41 (12.3)	30 (9.4)	53 (15.7)	24 (7.2)	157 (8.0)	151 (7.7)
Hypertension	13 (3.9)	6 (1.9)	15 (4.4)	23 (6.9)	-	-
Constipation	-	-	11 (3.3)	6 (1.8)	-	-
Epistaxis	-	-	4 (1.2)	7 (2.1)	-	-
Rhinitis	-	-	4 (1.2)	8 (2.4)	-	-
Productive cough	-	-	-	-	60 (3.1)	61 (3.1)
SAEs						
Patients with ≥ 1 SAE	45 (13.6)	54 (16.9)	63 (18.6)	56 (16.8)	342 (17.5)	336 (17.1)
Most Frequent SAEs (by PT)[b]						
Angina	2 (0.6)	1 (0.3)	-	-	5 (0.3)	8 (0.4)
COPD exacerbation	13 (3.9)	17 (5.3)	20 (5.9)	20 (6.0)	138 (7.1)	168 (8.5)
Cardiac failure	3 (0.9)	0 (0)	1 (0.3)	3 (0.9)	8 (0.4)	10 (0.5)
MI	1 (0.3)	3 (0.9)	1 (0.3)	3 (0.9)	7 (0.4)	10 (0.5)
Cardiac failure (congestive)	-	-	-	-	5 (0.3)	4 (0.2)
Pneumonia	7 (2.1)	2 (0.6)	7 (2.1)	4 (1.2)	31 (1.6)	48 (2.4)
Bronchitis	0 (0)	2 (0.6)	-	-	7 (0.4)	6 (0.3)
Abdominal pain	-	-	4 (1.2)	0 (0)	-	-
Chest pain	-	-	4 (1.2)	0 (0)	4 (0.2)	0 (0)
Pneumothorax	-	-	3 (0.9)	1 (0.3)	6 (0.3)	7 (0.4)
Upper respiratory tract infection	-	-	1 (0.3)	2 (0.6)	5 (0.3)	3 (0.2)
Lower respiratory tract infection	-	-	-	-	0 (0)	6 (0.3)
Lung neoplasm (malignant)	-	-	2 (0.6)	1 (0.3)	10 (0.5)	2 (0.1)
Cardiorespiratory arrest	-	-	-	-	4 (0.2)	1 (0.1)
Coronary artery disease	-	-	-	-	5 (0.3)	2 (0.1)
Myocardial ischemia	-	-	-	-	5 (0.3)	0 (0)
Diarrhea	-	-	-	-	0 (0)	5 (0.3)
Inguinal hernia	-	-	-	-	6 (0.3)	6 (0.3)
Gastroenteritis	-	-	-	-	1 (0.1)	6 (0.3)
Sepsis	-	-	-	-	4 (0.2)	2 (0.1)
Fall	-	-	-	-	5 (0.3)	4 (0.2)
Road traffic accident	-	-	-	-	4 (0.2)	1 (0.1)
Urinary retention	-	-	-	-	5 (0.3)	1 (0.1)
Benign prostatic hyperplasia	-	-	-	-	6 (0.3)	3 (0.2)
Acute respiratory failure	-	-	-	-	4 (0.2)	3 (0.2)
Dyspnea	-	-	-	-	11 (0.6)	4 (0.2)
Respiratory failure	-	-	-	-	9 (0.5)	11 (0.6)
WDAEs						
Patients with AEs leading to withdrawal	31 (9.3)	47 (14.7)	36 (10.7)	74 (22.2)	136 (7.0)	149 (7.6)
Most Common Reasons for Withdrawal (by PT)[b]						
COPD exacerbation	7 (2.1)	24 (7.5)	15 (4.4)	39 (11.7)	36 (1.8)	51 (2.6)
Dyspnea	2 (0.6)	4 (1.3)	0 (0)	15 (4.5)	9 (0.5)	21 (1.1)
Pneumonia	-	-	-	-	6 (0.3)	11 (0.6)
MI	-	-	0 (0)	3 (0.9)	4 (0.2)	4 (0.2)
Cardiac failure (congestive)	-	-	-	-	4 (0.2)	2 (0.1)

Harm	Study, n (%)					
	205.254		205.255		205.372	
	Tio R 5 N = 332	PL N = 319	Tio R 5 N = 338	PL N = 334	Tio R 5 N = 1,952	PL N = 1,965
Cardiorespiratory arrest	-	-	-	-	4 (0.2)	1 (0.1)
Renal failure	-	-	-	-	4 (0.2)	0 (0)
Bronchitis	-	-	-	-	0 (0)	5 (0.3)
Respiratory failure	-	-	-	-	3 (0.2)	8 (0.4)
Lung neoplasm (malignant)	-	-	-	-	5 (0.3)	1 (0.1)

AE = adverse event; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; PL = placebo; PT = preferred term; SAE = serious adverse event; Tio R 5 = Spiriva Respimat 5 mcg daily dose; WDAE = withdrawal due to AEs.
[a] Most frequent AEs were those reported by > 3% of patients in at least one of the treatment periods (note that the 3% may be in the Tio R 10 group which is not included in these data).
[b] Most frequent SAEs and WDAEs were those reported in > n = 3 patients in at least one treatment period.
Note: "-" means not reported by > 3% (AEs) or in > n = 3 patients (SAEs and WDAEs) in at least one treatment period.
Source: Clinical Study Report (CSR) 205.254,[4] CSR 205.255,[5] and CSR 205.372.[13]

In Study 205.452, the proportions of patients with AEs were similar between treatment groups (64.9% with Tio R 5 and 65.5% with Tio H 18). In this trial, AEs were only reported at the level of system organ class (Table 19). There did not appear to be any major imbalances in the proportions of patients with AEs within specific classes between the two treatment groups (Table 20).

TABLE 19: STUDY 205.452 (TIOSPIR) — OVERALL ADVERSE EVENT SUMMARY BY TREATMENT (TREATED SET)

Adverse Event	Treatment , n (%)	
	Tio R 5 N = 5,705	Tio H 18 N = 5,687
Patients with any AE,[a]	3,701 (64.9)	3,727 (65.5)
Patients with severe AEs	1,514 (26.5)	1,464 (25.7)
Patients with investigator-defined, drug-related AEs	374 (6.6)	374 (6.6)
Patients with WDAEs	468 (8.2)	498 (8.8)
Patients with SAEs	1,846 (32.4)	1,842 (32.4)

AE = adverse event; SAE = serious adverse event; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; Tio R 5 = Spiriva Respimat 5 mcg daily dose; WDAE = withdrawal due to AEs.
[a] Includes only outcome events, SAEs, AEs leading to discontinuation of trial drug, and AEs related to trial medication.
Note: A patient may be counted in more than one severity criterion.
Source: Clinical Study Report 205.452.[14]

TABLE 20: STUDY 205.452 (TIOSPIR) — FREQUENCY [N (%)] OF PATIENTS WITH INVESTIGATOR-DETERMINED, DRUG-RELATED AES BY TREATMENT AND PRIMARY SYSTEM ORGAN CLASS (TREATED SET)

System Organ Class	Treatment, n (%)	
	Tio R 5 N = 5,705	Tio H 18 N = 5,687
Patients with related AEs	374 (6.6)	374 (6.6)
Infections and infestations	21 (0.4)	24 (0.4)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)
Immune system disorders	4 (0.1)	1 (0.0)
Metabolism and nutrition disorders	2 (0.0)	3 (0.1)
Psychiatric disorders	9 (0.2)	6 (0.1)
Nervous system disorders	30 (0.5)	28 (0.5)

System Organ Class	Treatment, n (%)	
	Tio R 5 N = 5,705	Tio H 18 N = 5,687
Eye disorders	14 (0.2)	22 (0.4)
Ear and labyrinth disorders	2 (0.0)	0 (0.0)
Cardiac disorders	23 (0.4)	23 (0.4)
Vascular disorders	4 (0.1)	2 (0.0)
Respiratory, thoracic, and mediastinal disorders	165 (2.9)	161 (2.8)
Gastrointestinal disorders	123 (2.2)	129 (2.3)
Skin and subcutaneous tissue disorders	13 (0.2)	21 (0.4)
Musculoskeletal and connective tissue disorders	4 (0.1)	7 (0.1)
Renal and urinary disorders	17 (0.3)	20 (0.4)
Reproductive system and breast disorders	8 (0.1)	8 (0.1)
General disorders and administration site conditions	29 (0.5)	21 (0.4)
Investigations	1 (0.0)	2 (0.0)
Injury, poisoning, and procedural complications	1 (0.0)	1 (0.0)

AE = adverse event; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; Tio R 5 = Spiriva Respimat 5 mcg daily dose.
Notes: Treatment analysis — on-treatment plus 30-day follow-up.
Percentages were calculated using the total number of patients per treatment as the denominator.
Version 16.0 of MedDRA was used for reporting.
Source: Clinical Study Report 205.452.[14]

3.7.2 Serious Adverse Events

In studies 205.249 and 205.250, the proportions of patients with SAEs in the Tio R 5 groups (4.5% and 2.7%) were similar to those in the placebo groups (4.6% and 2.6%) as per Table 16. The proportions of patients with SAEs were numerically lower with Tio H 18 (3.6% and 1.3%). The most frequent SAEs were due to COPD exacerbations. In studies 205.251 and 205.252, the highest proportions of patients with SAEs were in the Iprat 36 groups (9.0% and 10.1%) compared with Tio R 5 (2.3% and 2.2%) and placebo (4.4% and 1.1%) as per Table 18. The most frequent SAEs, all of which were in the Iprat 36 groups, were due to COPD exacerbations (2.2%) and pneumonia (3.4%) in Study 205.251 and to atrial fibrillation (2.2%) and pulmonary edema (2.2%) in Study 205.252. In studies 205.254, 205.255, and 205.372, the proportion of patients with SAEs ranged from 13.6% to 18.6% with Tio R 5 and 16.8% to 17.1% with placebo (Table 19). The most frequent SAEs associated with Tio R 5 were COPD exacerbations (3.9% to 5.9%) and pneumonia (1.6% to 2.1%), compared with 5.3% to 6.0% and 0.6% to 2.4% with placebo, respectively. Urinary retention was reported as a SAE only in Study 205.372, occurring in 0.3% of patients treated with Tio R 5 and 0.1% of placebo-treated patients.

In Study 205.452, the proportions of patients with SAEs were similar between Tio R 5 (18.8%) and Tio H 18 (18.6%) as per Table 21. There were no statistically significant differences between treatment groups in the exposure-adjusted rates of SAEs by system organ class, as detailed in Table 21.

TABLE 21: STUDY 205.452 (TIOSPIR) — EXPOSURE-ADJUSTED INCIDENCE RATES OF SAES BY TREATMENT WITH INCIDENCE OF 10 OR MORE PATIENTS IN ANY TREATMENT GROUP AT THE LEVEL OF SOC (TS)

System Organ Class	Treatment , n				
	Tio R 5		Tio H 18		Tio R 5 vs. Tio H 18
	N	Rate[a]	N	Rate[a]	Rate Ratio (95% CI)
Number of patients	5,705		5,687		
Total treated with SAE events	1,846	18.8	1,842	18.6	1.01 (0.95 to 1.08)
Blood and lymphatic system disorders	16	0.1	29	0.2	0.55 (0.30 to 1.01)
Cardiac disorders	273	2.4	270	2.3	1.01 (0.85 to 1.20)
Eye disorders	21	0.2	19	0.2	1.10 (0.59 to 2.06)
Gastrointestinal disorders	148	1.3	140	1.2	1.06 (0.84 to 1.33)
General disorders and administration site conditions	99	0.8	111	0.9	0.89 (0.68 to 1.17)
Hepatobiliary disorders	28	0.2	26	0.2	1.08 (0.63 to 1.84)
Infections and infestations	502	4.4	495	4.4	1.02 (0.90 to 1.15)
Injury, poisoning, and procedural complications	93	0.8	97	0.8	0.96 (0.72 to 1.27)
Metabolism and nutrition disorders	40	0.3	31	0.3	1.29 (0.81 to 2.06)
Musculoskeletal and connective tissue disorders	63	0.5	82	0.7	0.77 (0.55 to 1.06)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	274	2.4	250	2.2	1.10 (0.93 to 1.30)
Nervous system disorders	138	1.2	121	1.0	1.14 (0.89 to 1.46)
Psychiatric disorders	31	0.3	21	0.2	1.48 (0.85 to 2.57)
Renal and urinary disorders	65	0.6	59	0.5	1.10 (0.78 to 1.57)
Reproductive system and breast disorders	17	0.1	14	0.1	1.21 (0.60 to 2.46)
Respiratory, thoracic, and mediastinal disorders	957	8.9	964	8.9	1.00 (0.91 to 1.09)
Surgical and medical procedures	47	0.4	48	0.4	0.98 (0.65 to 1.46)
Vascular disorders	92	0.8	91	0.8	1.01 (0.76 to 1.35)

CI = confidence interval; SAE = serious adverse event; SOC = system organ class; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; Tio R 5 = Spiriva Respimat 5 mcg daily dose.

[a] Rate = Rate of first occurrence per 100 patient-exposure years (PEY). PEY is defined as patient-years at risk calculated from the start of treatment to 30 days after last dose of study drug.

Source: Clinical Study Report 205.452.[14]

3.7.3 Withdrawals Due to Adverse Events

In studies 205.249 and 205.250, the proportions of patients with WDAEs in the Tio R 5 groups (2.7% and 1.3%, respectively) and Tio H 18 groups (3.6% and 0%, respectively), were numerically lower than with placebo (2.6% and 11.1%, respectively) as per Table 16. The most frequent WDAEs were due to COPD exacerbations and dyspnea-related causes (i.e., in the placebo group of Study 205.249 these occurred in 2.8% and 4.7% of patients, respectively). In studies 205.251 and 205.252, the highest proportions of patients overall with WDAEs were in the Iprat 36 groups (12.4% and 10.1%, respectively) compared with Tio R 5 (6.8% and 7.6%, respectively) and placebo (5.5% and 12.2%, respectively), as per Table 18. The most common reason for WDAEs was COPD exacerbations across all treatment groups. There were two patients (2.2%) in the Iprat 36 group of Study 205.252 who withdrew due to atrial fibrillation. In studies 205.254, 205.255, and 205.372, the proportion of patients with WDAEs ranged from 7.0% to 10.7% with Tio R 5, and 7.6% to 22.2% with placebo (Table 19). The most common reasons for WDAEs were COPD exacerbations ranging from 1.8% to 4.4% with Tio R 5, and from 2.6% to 11.7% with placebo.

Pneumonia was the cause of WDAEs in 0.3% of Tio R 5-treated patients and 0.6% of placebo-treated patients in Study 205.372.

In Study 205.452, the proportions of patients with WDAEs were similar between Tio R 5 (8.2%) and Tio H 18 (8.8%), as per Table 22. There did not appear to be any imbalances between treatment groups in the proportion of patients with WDAEs when frequency by system organ class was investigated, as detailed in Table 22.

TABLE 22: STUDY 205.452 (TIOSPIR) — FREQUENCY [N (%)] OF PATIENTS WITH WDAES BY TREATMENT AND PRIMARY SYSTEM ORGAN CLASS (TS)

System Organ Class	Treatment, n (%)	
	Tio R 5 N = 5,705	Tio H 18 N = 5,687
Patients with WDAEs	468 (8.2)	498 (8.8)
Infections and infestations	53 (0.9)	51 (0.9)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	65 (1.1)	79 (1.4)
Blood and lymphatic system disorders	0 (0.0)	1 (0.0)
Immune system disorders	3 (0.1)	1 (0.0)
Metabolism and nutrition disorders	3 (0.1)	3 (0.1)
Psychiatric disorders	10 (0.2)	6 (0.1)
Nervous system disorders	35 (0.6)	24 (0.4)
Eye disorders	3 (0.1)	7 (0.1)
Ear and labyrinth disorders	2 (0.0)	1 (0.0)
Cardiac disorders	40 (0.7)	40 (0.7)
Vascular disorders	7 (0.1)	7 (0.1)
Respiratory, thoracic, and mediastinal disorders	175 (3.1)	198 (3.5)
Gastrointestinal disorders	39 (0.7)	31 (0.5)
Hepatobiliary disorders	0 (0.0)	1 (0.0)
Skin and subcutaneous tissue disorders	11 (0.2)	16 (0.3)
Musculoskeletal and connective		
Tissue disorders	5 (0.1)	7 (0.1)
Renal and urinary disorders	9 (0.2)	12 (0.2)
Reproductive system and breast disorders	5 (0.1)	4 (0.1)
Congenital, familial, and genetic disorders	0 (0.0)	1 (0.0)
General disorders and administration site conditions	21 (0.4)	27 (0.5)
Investigations	2 (0.0)	1 (0.0)
Injury, poisoning, and procedural complications	6 (0.1)	13 (0.2)
Surgical and medical procedures	2 (0.0)	1 (0.0)

Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; Tio R 5 = Spiriva Respimat 5 mcg daily dose; WDAE = withdrawal due to adverse event.
Notes: Treatment analysis — on-treatment plus 30-day follow-up.
Percentages were calculated using the total number of patients per treatment as the denominator.
Source: Clinical Study Report 205.452.[14]

3.7.4 Mortality

As mortality was a key efficacy outcome in the review protocol, the results for this outcome are reported in Section 3.6.1, and detailed outcome data are provided in APPENDIX 4: .

3.7.5 Notable Harms

As per the review protocol, notable harms include CV AEs, pneumonia, and anticholinergic AEs. The proportions of patients with pneumonia and anticholinergic AEs (e.g., dry mouth, urinary retention) have been presented in the previous sections on AEs, SAEs, and WDAEs. Overall, the frequency of CV-related AEs was low across the included trials. In Study 205.452, additional safety analyses were conducted related to CV-related AEs, which included analyses of the incidence of MACE, stroke, MIs, and TIAs, as detailed in Table 23 to Table 26. In all analyses, no statistically significant differences were found between Tio R 5 and Tio H 18 for any of the outcomes.

TABLE 23: STUDY 205.452 (TIOSPIR) — INCIDENCE OF MACE AND ANALYSIS TIME TO ONSET OF FIRST MACE BY TREATMENT (TS, ON-TREATMENT ONLY)

MACE	Treatment, n (%)	
	Tio R 5 (N = 5,705)	Tio H 18 (N = 5,687)
Patients with MACE[a]	222 (3.9)	202 (3.6)
Comparison vs. Tio H 18		
HR (95% CI); *P* value	1.100 (0.909 to 1.331); *P* = 0.3263	

CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiovascular event; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; Tio R 5 = Spiriva Respimat 5 mcg daily dose; TS = treated set.
[a] Causes of death from MACE were determined by adjudication.
Source: Clinical Study Report 205.452.[14]

TABLE 24: STUDY 205.452 (TIOSPIR) — ANALYSIS OF TIME TO FIRST STROKE BY TREATMENT (TS, ON-TREATMENT ONLY)

Stroke	Treatment, n (%)	
	Tio R 5 (N = 5,705)	Tio H 18 (N = 5,687)
Patients with stroke	52 (0.9)	57 (1.0)
Comparison vs. Tio H 18		
HR (95% CI); *P* value	0.911 (0.625 to 1.326); *P* = 0.6253	

CI = confidence interval; DAS = death analysis set; HR = hazard ratio; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; Tio R 5 = Spiriva Respimat 5 mcg daily dose; TS = treated set.
Note: Stroke excludes transient ischemic attack.
Source: Clinical Study Report 205.452.[14]

TABLE 25: STUDY 205.452 (TIOSPIR) — ANALYSIS OF TIME TO FIRST MI BY TREATMENT (TS, ON-TREATMENT ONLY)

MI	Treatment , n (%)	
	Tio R 5 (N = 5,705)	Tio H 18 (N = 5,687)
Patients with MI	73 (1.3)	52 (0.9)
Comparison vs. Tio H 18		
HR (95% CI); *P* value	1.405 (0.984 to 2.004); *P* = 0.0612	

CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; Tio R 5 = Spiriva Respimat 5 mcg daily dose; TS = treated set.
Source: Clinical Study Report 205.452.[14]

TABLE 26: STUDY 205.452 (TIOSPIR) — ANALYSIS OF TIME TO FIRST TIA BY TREATMENT (TS, ON-TREATMENT ONLY)

TIA	Treatment, n (%)	
	Tio R 5 (N = 5,705)	Tio H 18 (N = 5,687)
Patients with TIA	30 (0.5)	20 (0.4)
Comparison vs. Tio H 18		
HR (95% CI); *P* value	1.502 (0.853 to 2.645); *P* = 0.1587	

CI = confidence interval; HR = hazard ratio; TIA = transient ischemic attack; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; Tio R 5 = Spiriva Respimat 5 mcg daily dose; TS = treated set.
Source: Clinical Study Report 205.452.[14]

4. DISCUSSION

4.1 Summary of Available Evidence

Eight prospective, DB RCTs met the selection criteria for inclusion in the systematic review: studies 205.249 (N = 131),[1] 205.250 (N = 76),[2] 205.251 (N = 361),[3] and 205.252 (N = 358), 205.254 (N = 983),[4] 205.255 (N = 1,007),[5] 205.372, (N = 3,991), and 205.452 (TIOSPIR) (N = 17,183). All trials included patients who were at least 40 years of age, had a diagnosis of moderate-to-severe COPD (by ECCS criteria), and a history of smoking (at least 10 pack-years). The primary efficacy outcome in studies 205.249, 205.250, 205.251, and 205.252 was trough FEV_1 response. In studies 205.254 and 205.255, there were four co-primary end points (trough FEV_1 response, SGRQ, TDI, and COPD exacerbations). There were two co-primary end points in each of Study 205.372 (trough FEV_1 response and time to first COPD exacerbation) and Study 205.452 (time to death from any cause and time to first COPD exacerbation). All efficacy end points were analyzed using the FAS population or FAS subsets, depending upon outcome. A key limitation among the applicable trials is the uncertainty regarding the clinical significance of the results and methodology used to establish the non-inferiority margin of 0.05 L for trough FEV_1 response. Other important limitations are baseline characteristics (e.g., underrepresentation of female patients, predominance of Caucasian patients) and study design factors (e.g., exclusion from the majority of trials of patients who had previously received tiotropium, use of a less-than-optimal dose of ipratropium), which limit the generalizability of the study findings to Canadian COPD patients.

4.2 Interpretation of Results

4.2.1 Efficacy

Tiotropium is an orally inhaled LAMA in a dry powder capsule inhaler delivery form as Spiriva HandiHaler (18 mcg once daily) that has been approved in Canada since 2002. There is a large body of evidence supporting the efficacy and safety of tiotropium delivered through the HandiHaler device, which is reflected in the recommendation for its use in the CTS clinical practice guidelines in combination with SABAs, LABAs alone, or ICS/LABA combinations, depending upon the severity of COPD.[16,17] Spiriva Respimat (5 mcg once daily as two actuations of 2.5 mcg) is a new multi-dose, propellant-free formulation of Spiriva that contains tiotropium in an oral inhalation solution that is delivered through a Soft Mist Inhaler. Both Spiriva HandiHaler and Spiriva Respimat have similar Health Canada–approved indications for the long-term, once-daily maintenance treatment of airflow obstruction in patients with COPD, with the exception that Spiriva Respimat is also indicated for the reduction of exacerbations.[6,7] Thus, the key consideration is how do the two delivery forms of Spiriva compare? The clinical trials that are the best suited to answer this question are those in which the HandiHaler device and the Respimat inhaler have been directly compared, which are studies 205.249, 205.250, and 205.452 (TIOSPIR).

Studies 205.249 and 205.250 were identical crossover, multi-centre, DB RCTs that compared four 4-week treatment periods of Tio R 5, Tio R 10 (not reported), Tio H 18, and placebo in patients with moderate-to-severe COPD. The primary efficacy outcome was trough FEV_1 response at the end of four weeks. The superiority of both Tio R 5 and Tio H 18 compared with placebo on trough FEV_1 response was demonstrated in the FAS population in both trials. In keeping with the stepwise statistical comparison, the non-inferiority (also based on trough FEV_1 response) of Tio R 5 and Tio H 18 was then examined. Non-inferiority was concluded, as the treatment differences in trough FEV_1 response did not exceed the pre-specified non-inferiority threshold of 0.050 L chosen by the manufacturer. As described in detail in Section 3.5: Critical Appraisal, the clinical significance and methodology used to establish the non-inferiority margin is unclear. The magnitude of the treatment differences in trough FEV_1 response did exceed the MCID of 0.100 L for Tio R 5 versus placebo in both studies. A PP analysis confirmed that the treatment differences were the same, with the same findings of non-inferiority of Tio R 5 and Tio H 18. As the active ingredient (tiotropium) is the same in both products and both were shown to exceed the MCID for trough FEV_1 response that was statistically significant when compared with placebo, it is likely that non-inferiority of the products can be concluded based on these studies.

TIOSPIR was a large-scale, multi-centre, parallel-group DB RCT that compared the efficacy and safety of Tio R 2.5 (not reported), Tio R 5, and Tio H 18 in patients with COPD. The purpose of this trial was to provide prospective data from a trial of adequate size and duration to establish that, compared with tiotropium administered through the HandiHaler, tiotropium administered through Respimat has (a) similar effects on mortality and (b) similar or superior effects on COPD exacerbations. Results from Study 205.372 had shown not only a risk of COPD exacerbations that appeared to be numerically similar or potentially superior to that observed in the UPLIFT trial with the HandiHaler device,[8,9] but also an HR for fatal events that was unexpectedly higher than in the UPLIFT trial, although the CIs from the two studies overlapped at comparable time points. TIOSPIR was designed to test for non-inferiority on the co-primary end point of time to death (all-cause mortality) and superiority for the second co-primary end point of time to first COPD exacerbation. In addition, a subset of patients from TIOSPIR participated in a SSS in which the non-inferiority of Tio R 5 and Tio H 18 was examined for the key secondary end point of trough FEV_1 based on the lower limit of the 95% CI of the treatment difference not lying below 0.05 L. Non-inferiority of Tio R 5 and Tio H 18 was concluded in TIOSPIR based on the results which met this pre-specified non-inferiority margin.

A key efficacy outcome for this review was mortality (all-cause and CV-related). Very few deaths were reported in the included trials of shorter duration (205.249, 205.250, 205.251, and 205.252); however, the number of deaths was higher in the trials of longer duration (205.254 and 205.255), and there was suggestion of an imbalance in the number of deaths associated with Tio R 5. As reported in detail in Appendix 6: Summary and Appraisal of Mixed Treatment Comparison, a mixed treatment comparison (MTC) by Dong et al.[11] compared the risks of all-cause mortality and CV deaths for Spiriva Respimat, Spiriva HandiHaler, LABAs, ICS, and ICS/LABA combinations in patients with COPD. Based on an MTC, the authors reported that Spiriva Respimat was associated with a universally increased risk of all-cause death compared with placebo, Spiriva HandiHaler, LABA, and ICS/LABA combinations.[11] The risk of death from CV causes was also statistically significantly increased for Spiriva Respimat compared with placebo, Spiriva HandiHaler, LABA, ICS/LABA combinations, or ICS alone.[11] There are various limitations associated with the MTC as detailed in Appendix 6, including a possible dose-response association due to inclusion of Tio R 10, the assessment of rare events within relatively short-duration trials, and an uncertain baseline risk given most (if not all) of the included studies excluded patients with significant diseases (i.e., specifically CV morbidities).

The apparent imbalance in the number of deaths led to the undertaking of Study 205.372 in approximately 4,000 patients with COPD. At study completion, there were 52 deaths (2.7%) in the Tio R 5 group and 38 deaths (1.9%) in the placebo group over one year. Although there were more deaths in the Tio R 5 group, an analysis of fatal events revealed a non-statistically significant rate ratio of all fatal events, as well as rate ratios of fatal events due to cardiac disorders, lower respiratory system disorders, or other respiratory system disorders. Nonetheless, the rate ratios for fatal events was unexpectedly higher than previously observed in the UPLIFT trial,[8,9] although the CIs from the two studies overlapped at comparable time points. To further investigate the safety of Spiriva Respimat, the large-scale TIOSPIR study in approximately 17,000 patients was initiated, with an observation period of up to three years to provide prospective data from a trial of adequate size and duration to show that Tio R 5 and Tio H 18 have similar effects on all-cause mortality. At study completion, there had been 423 deaths (7.4%) in the Tio R 5 group and 439 deaths (7.7%) in the Tio H 18 group over the three years. The corresponding HR was 0.957 (95% CI, 0.837 to 1.094) which met the pre-specified non-inferiority margin for the HR of all-cause death of the upper 95% CI not exceeding 1.25. An analysis of the causes of death by system organ class in TIOSPIR did not reveal any statistically significant differences between treatments for any classification. As the UPLIFT trial had shown a similar mortality in patients on Tio H 18 compared with placebo, Health Canada concluded that the results from the TIOSPIR study (205.452) provide sufficient evidence to alleviate the concerns about an increased mortality risk with Spiriva Respimat.[10]

The analysis of COPD exacerbations in TIOSPIR revealed that very similar proportions of patients in the Tio R 5 and the Tio H 18 groups experienced COPD exacerbations, corresponding with a non-statistically significant HR of 0.978 (95% CI, 0.928 to 1.032). Accordingly, the proportions of patients who had moderate-to-severe COPD exacerbations, or who had hospitalizations due to COPD exacerbations, were also very similar between treatment groups, corresponding with non-statistically significant HRs of 0.983 (95% CI, 0.932 to 1.037) and 1.024 (95% CI, 0.929 to 1.128), respectively. The comparison of trough FEV_1 response through 120 weeks in the TIOSPIR SSS patients demonstrated that Tio R 5 was non-inferior to Tio H, based on the pre-specified non-inferiority margin of –0.050 L (adjusted mean treatment difference of –0.010 L [95% CI, –0.038 to 0.018]).

The other included trials compared Tio R 5 with placebo (studies 205.254, 205.255, and 205.372) and with placebo and ipratropium bromide 36 mcg four times daily (studies 205.251 and 205.252) on various outcomes (e.g., COPD exacerbations, SGRQ, COPD symptoms, and trough FEV_1 response). The results of studies 205.254, 205.255, and 205.372 support that, compared with placebo, Tio R 5 is associated with statistically significant reductions in COPD exacerbations, moderate-to-severe COPD exacerbations, time to first COPD exacerbation, and hospitalizations due to COPD exacerbations. In studies 205.254, 205.255, and 205.372, Tio R 5 was associated with statistically significant improvements in SGRQ total scores and domain scores over one year of treatment. Of note, the magnitude of the treatment differences between Tio R 5 and placebo did not reach the MCID for SGRQ total score (a difference of ≥ 4 points) in any of the three trials. In studies 205.251 and 205.252, statistically significant differences in COPD symptom scores between Tio R 5 and placebo or Iprat 36 were not reported for all symptoms, and results were inconsistent between the two trials. This may be due to the short duration of the trials (12 weeks); however, according to the clinical expert involved in the review, the effect of treatment on COPD symptoms should have been realized within this time frame. In contrast, in studies 205.254 and 205.255, statistically significant treatment differences at the end of 48 weeks of treatment were found for all comparisons of Tio R 5 versus placebo for all COPD symptoms. In addition, statistically significant treatment differences in Mahler TDI focal scores between Tio R 5 and placebo were also observed, and the differences exceeded the MCID (improvement of at least one unit from the BDI) in both studies.

In studies 205.251 and 205.252, treatment differences in trough FEV_1 response at the end of 12 weeks were statistically significant in favour of Tio R 5 compared with placebo, and the magnitude of the treatment differences in trough FEV_1 response exceeded the MCID in both studies. In contrast, treatment differences between Iprat 36 and placebo did not reach statistical significance, and the treatment differences between Iprat 36 and placebo did not exceed the MCID for trough FEV_1 response in either study. Non-inferiority of Tio R 5 with Iprat 36 was demonstrated in both trials, based on the pre-specified non-inferiority margin of 0.05 L. Tio R 5 also demonstrated superiority versus Iprat 36 in Study 205.252, but not in Study 205.251. Overall, the reason for these observations (i.e., lack of superiority for Iprat 36 over placebo and superiority of Tio R 5 over Iprat 36 in only one study) is unclear, although it may have been due to the use of a less-than-optimal dose of ipratropium in these trials. According to the clinical expert involved in the review, in clinical practice a dose of twice this magnitude (72 mcg four times a day) has been used. This may have implications for the generalizability of data from these trials to the Canadian COPD population, if the dose of Iprat 36 used in the trials does not reflect current clinical practice. In studies 205.254, 205.255, and 205.372, the treatment differences between Tio R 5 and placebo in trough FEV_1 response at the end of the 48-week treatment periods were statistically significant in all three trials. The magnitude of the treatment differences between Tio R 5 and placebo all exceeded the MCID of 0.100 L.

Across all trials, the use of rescue medication (salbutamol MDI as needed) was similar between Tio R 5 and Tio H 18, and was less than with placebo treatment. Patient compliance or adherence to study medication was high across all included studies (i.e., compliance measured as medication taken [% prescribed]) was > 95% with all devices (Respimat, HandiHaler, or MDI). In Study 205.252, a patient satisfaction questionnaire was administered at US study sites. Overall, there was a high degree of satisfaction with both the Respimat inhaler and the MDI. There were statistically significant differences in favour of the Respimat device in the ability to tell the amount of medication left in the container, inhaler durability, and the environmentally friendly nature of the inhaler, and higher satisfaction with the MDI in the overall convenience of carrying the inhaler. These results should be viewed with caution, due to the small sample size (n = 46 to 53, depending on attribute). The results of two small observational studies[43,44] that assessed patient preferences for, and switching between, the Respimat and HandiHaler devices are summarized in Appendix 7: Comparison of Inhaler Devices for Spiriva Respimat and Spiriva Handihaler.

In studies with co-primary end points (205.254, 205.255, 205.372, and TIOSPIR), results were consistent with regard to the statistical significance of the co-primary end points within trials, thus providing confidence in the results. In studies 205.254 and 205.255, the treatment differences in the four co-primary end points of trough FEV_1 response, SGRQ, Mahler TDI scores, and COPD exacerbations were all statistically significant in favour of Tio R 5; however, the MCID of ≥ 4 points was not achieved for SGRQ total score. In Study 205.372, the two co-primary end points of trough FEV_1 response and time to first COPD exacerbation were also both statistically significant in favour of Tio R 5. Lastly, in TIOSPIR, the two co-primary end points of time to all-cause death and time to first COPD exacerbation were consistent in that, for both end points, there was no statistically significant difference between Tio R 5 and Tio H 18.

As detailed in Appendix 1: Patient Input Summary, outcomes important to patients with COPD are symptom relief, impact on activities of daily living, caregiver burden, and the challenges associated with compliance and correct use of inhalers or devices. Of these, the only outcome that was addressed in the included trials was COPD symptoms, although as discussed previously, the data are limited and the results were inconsistent between identical trials.

4.2.2 Harms

In the included trials that directly compared Tio R 5 with Tio H 18, the proportions of patients with treatment-emergent AEs, SAEs, and WDAEs were very similar between the treatment groups. Overall, the most frequently reported AEs across all included trials were COPD exacerbations, nasopharyngitis, and dyspnea-related events. More patients in the Tio R 5 groups of the trials experienced dry mouth, which the clinical expert advised is to be expected with tiotropium. There did not appear to be any clear association of pneumonia AEs with any one treatment. In Study 205.252, 3.4% of patients in the Iprat 36 group and no patients in the Tio R 5 or placebo groups had an AE of atrial fibrillation, which was also not reported in any other treatment group. In this study, two patients (2.2%) in the Iprat 36 group discontinued the study due to atrial fibrillation. According to the product labelling, atrial fibrillation is a recognized, undesirable cardiac side effect of ipratropium, along with palpitations, supraventricular tachycardia, and increased heart rate. COPD exacerbations were the most frequently reported SAEs and the most common reason for WDAEs across all treatment groups and trials. Overall, the frequency of CV-related AEs was low across the included trials. In Study 205.452, additional safety analyses were conducted related to CV-related AEs, which included analyses of the incidence of MACE, stroke, MI, and TIAs. In all analyses, there were no statistically significant differences found between Tio R 5 and Tio H 18 for any of these outcomes. Of note, in Study 205.452, patients who had been previously treated with tiotropium were eligible to enter the trials. It follows that these patients may have been at low risk of cardiac AEs if they had previously been treated with tiotropium and were able to tolerate the treatment with no adverse cardiac effects.

Overall, the harms results support that Tio R 5 and Tio H 18 have comparable safety and tolerability profiles. Despite the suggestion of an increased mortality risk with Spiriva Respimat, it was demonstrated in the large-scale TIOSPIR study (205.452) that the proportions of deaths between Tio R 5 and Tio H 18 were similar over a three-year period. This led Health Canada to conclude that the results from the TIOSPIR study (205.452) provide sufficient evidence to alleviate the concerns about an increased mortality risk with Spiriva Respimat.[10]

5. CONCLUSIONS

Eight prospective, DB RCTs met the selection criteria for inclusion in the review, three of which directly compared Tio R 5 and Tio H 18 in patients with moderate-to-severe COPD. A key limitation is the uncertainty regarding the clinical significance of the results and the methodology used to establish the non-inferiority margin of 0.05 L for trough FEV_1 response in some of the trials. Other limitations are baseline characteristics and study design factors which limit the generalizability of the study findings to Canadian COPD patients. Based on the non-inferiority margin for trough FEV_1 response pre-specified by the manufacturer, Tio R 5 was shown to be non-inferior to Tio H 18. Tio R 5 was also shown to have similar effects on reducing COPD exacerbations when compared with Tio H 18. Results from other included trials support that Tio R 5 is superior to placebo in reducing COPD exacerbations, improving QoL (SGRQ total score), improving TDI focal scores, and improving various COPD symptoms. The harms data supports that Tio R 5 and Tio H 18 have similar safety profiles, as the proportions of patients with AEs, SAEs, and WDAEs with each treatment were similar. The most frequently reported AE regardless of treatment, which was also the most frequent SAE and reason for WDAEs, was COPD exacerbations. Despite the suggestion of an increased mortality risk with Spiriva Respimat based on early trials and a mixed treatment comparison (MTC)[11] that compared Spiriva Respimat and Tio H 18, LABA, ICS/LABA combinations, and ICS alone, it was shown in the prospective, large-scale TIOSPIR study that the proportions of deaths between Tio R 5 and Tio H 18 were similar over a three-year period.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH Common Drug Review (CDR) staff based on the input provided by patient groups. It has not been systematically reviewed.

1. Brief Description of Patient Group(s) Supplying Input

Four patient groups, the Ontario Lung Association (OLA), the Lung Association of Saskatchewan (LAS), the British Columbia Lung Association (BCLA), and the Lung Association, Alberta & NWT (TLA) submitted their inputs for this review.

OLA is a charity that supports patients with lung disease and their caregivers, provides resources to health care providers (HCPs), and invests in lung research. It also advocates for the prevention of respiratory illness, tobacco cessation, and improved air quality. OLA has received funding from Pfizer, GlaxoSmithKline (GSK), Boehringer Ingelheim, AstraZeneca, Merck, Novartis, Takeda, InterMune, Grifols, Actelion, Astellas Pharma, Bayer, Johnson & Johnson (J&J), Roche, Rx&D, Valeant Pharmaceuticals, Eli Lilly, and the Ontario Home Respiratory Services Association.

LAS is a charity that provides support to patients with lung disease and their caregivers. Its role is to improve respiratory health and the overall quality of life through programs, evidence-based education, research, training, treatment, advocacy, and prevention of lung disease. LAS provides patient education through a COPD Helpline staffed by HCPs who are Certified Respiratory Educators (CREs). LAS implements COPD awareness campaigns and conducts public telehealth and webinars on COPD. LAS has received funding from AstraZeneca, Boehringer Ingelheim, GSK, Grifols, InterMune, Merck Frosst, Novartis, Nycomed, Pfizer, Roche, and Takeda.

BCLA is a charity whose role is to improve respiratory health and overall quality of life through programs, education, research, training, treatment, advocacy, and the prevention of lung diseases. BCLA's staff and volunteers include HCPs, patients, and individuals with training and experience in lung health. BCLA funds research on lung diseases. BCLA has received funding from Grifols, GSK, InterMune, AstraZeneca, Boehringer Ingelheim, Pfizer, Novartis, and Merck Frosst.

TLA is a charity with a mission to prevent lung disease and promote lung health. TLA provides resources and support for patients, families, communities, and employers to improve lung health. TLA shares concerns over air quality to governments and supports individuals to quit tobacco use. It also funds medical research. TLA has received funding from Pfizer, GSK, Merck Frosst, Novartis, Grifols, Astra Zeneca, and Boehringer Ingelheim. TLA also shares partnership with J&J on a tobacco cessation program.

No conflicts of interests were declared by any of these organizations with regard to this submission.

2. Condition and Current Therapy-Related Information

Patient groups gathered information from COPD patients, family members, and caregivers through online surveys, phone interviews, and direct one-on-one conversations. Information from CREs and the scientific literature was also included.

COPD — a progressively debilitating disease with treatment but no cure — affects almost all aspects of daily living, including physical and leisure activities, as well as relationships with family and friends. It impacts basic activities like dressing, cooking, hygiene care, climbing stairs, and travelling. Most patients

are declined travel insurance. The most commonly experienced symptoms are fatigue and shortness of breath (which may occur even at rest in severe cases), followed by mucus, wheezing, frequent chest infections, and coughing. Patients often feel prematurely old and COPD was said to "slowly rob people of independence."

The inability to perform daily activities results in depression, hopelessness, frustration, and loss of self-worth for some. Even carrying groceries can take several trips. One patient commented, "It is a constant fight to maintain independence and reduce depression." Another patient noted weight gain as a result of COPD. Patients may feel they are burdening their family. Many patients have to leave the work force, which can affect them financially. Patients reported constantly needing medications, and as the condition worsens they may take multiple medications and potentially be on supplementary oxygen therapy. Although oxygen has often benefited patients, being "tethered" to oxygen tubing restricts mobility and patients feel uncomfortable in social situations. Patients also reported experiencing two-to-three flare-ups per year on average, resulting in lung function decline. Flare-ups are also among the top reasons for hospitalization. Patients may concurrently have malnutrition, cardiovascular problems, loss of muscle and bone density, and lung cancer.

Caregivers experience similar negative impacts. Caring for COPD patients affects their work, social relationships, physical and leisure activities, independence, and ability to travel and socialize. They have to take time off work to run errands and to attend frequent medical appointments. Caregivers also face financial challenges, depending on level of reimbursement for medicines and also due to expenses incurred from assistive devices and home modifications for patients. They feel exhausted, socially isolated, depressed, and have a limited ability to manage their own physical and mental well-being.

Interviewed patients had experience with Spiriva, Advair, Symbicort, Daxas, prednisone, Ventolin, Atrovent, Serevent, Seebri, and Onbrez; a few had recently tried Breo Ellipta. Current treatments provide some relief for fatigue, shortness of breath, cough, appetite loss, low energy, and inability to fight infection. However, adverse effects such as palpitations, dry mouth, mouth sores, vision problems, urinary problems, and impact on mood need to be better managed. Identifying a device that can effectively deliver medication — especially given the challenges associated with compliance and incorrect use of inhalers — would be of significant benefit. There was a desire for fewer medical appointments and less cost burden.

3. Related Information About the Drug Being Reviewed

Patients from LAS, BCLA, and TLA reported no experience with tiotropium in the Spiriva Respimat formulation. All patients from OLA had used Spiriva in various administrative devices (patients had used either Combivent or Respimat) and rated it as equivalent to other treatments in terms of administration, time required for treatment, costs, and adverse effects. In terms of treatment, one patient rated it as better than other treatments, while the rest rated it as equivalent. Swelling of hands, feet, and joints was identified as the least bearable side effect by multiple patients on this treatment.

Patients indicated that some adverse effects are acceptable as long as it is nothing irreversible or worse than what they are currently experiencing. One patient commented, "Most side effects would be bearable if I could just breathe a bit better and could wake up with enough energy to get through the day."

Symptoms that patients would most like to improve are shortness of breath, fatigue, coughing, and appetite. Patients would like to improve daily functioning and be less oxygen-dependent. However, patients are interested in therapies that go beyond symptom relief. They would like to have greater

independence and energy levels, an increased ability to fight infections, better lung function, fewer exacerbations and hospitalizations, and improved health-related quality of life. In addition, patients would like to have less or no cost burden associated with new treatments.

In summary, four patients groups (OLA, LAS, BCLA, and TLA) submitted their input for this review. All groups said that the current therapies for COPD still do not meet all patients' needs, such as sometimes not having enough symptom relief (cough, shortness of breath). Adverse effects such as palpitations, dry mouth, mouth sores, vision problems, and urinary problems need to be better managed. In addition, compliance with current therapy depends in part on the ease of use of the inhaler device. Patients want to be less of a burden to their families. They do not want to make additional changes in their daily routines for themselves or their caregivers.

Although only patients in Ontario had the experience with the treatment of Spiriva Respimat, all four patient groups expect to have access to the new drugs and to improve overall the management of their COPD.

APPENDIX 2: LITERATURE SEARCH STRATEGY

Overview	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	February 9, 2015
Alerts:	Bi-weekly search updates until project completion
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded
Syntax Guide	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

Multi-database Strategy
1 spiriva* respimat*.mp. (12)
2 (Spiriva* or tiotropium or BA 679 BR or BA 679BR or BA-679 BR).ti,ab,rn,nm,sh,hw,ot. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, ui] (4711)
3 136310-93-5.rn,nm. (3059)
4 2 or 3 (4711)
5 (Respimat* or spray or mist or solution).ti,ab,rn,nm,sh,hw,ot. (932488)
6 4 and 5 (276)
7 1 or 6 (280)
8 7 use pmez (70)
9 *tiotropium bromide/ (922)
10 (Spiriva* or tiotropium* or BA 679 BR or BA 679BR or BA-679 BR or UNII-XX112XZP0J).ti,ab. (2524)
11 (Respimat* or spray or mist or solution).ti,ab. (843902)
12 (9 or 10) and 11 (219)
13 conference abstract.pt. (1746506)
14 12 not 13 (151)
15 14 use oemezd (84)
16 8 or 15 (154)
17 remove duplicates from 16 (96)
18 exp animals/ (37471448)
19 exp animal experimentation/ or exp animal experiment/ (1835408)
20 exp models animal/ (1235480)
21 nonhuman/ (4443642)
22 or/18-21 (38741712)
23 exp humans/ (29160255)
24 exp human experimentation/ (345380)
25 exp human experiment/ (333734)
26 23 or 24 or 25 (29162332)
27 22 not 26 (9580965)
28 17 not 27 (93)

Other Databases	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	January 2015
Keywords:	Spiriva Respimat, Tiotropium, COPD
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters), were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Hohlfeld et al., 2014[45]	Inappropriate design
Hodder et al., 2011[35]	Inappropriate design
Bateman et al., 2010[15]	Inappropriate design
Voshaar et al., 2008[34]	Inappropriate design
Rennard et al., 2014[46]	Inappropriate design
Tang et al., 2013[47]	Inappropriate design
Ichinose et al., 2010[48]	Inappropriate design
Caillaud et al., 2007[49]	Inappropriate design
Ma et al., 2014[50]	Unable to obtain

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 27: STUDIES 205.249, 205.250, 205.251, AND 205.252 — ANALYSIS OF DEATHS BY TREATMENT (SAFETY SET)

Characteristic	Study							
	205.249		205.250		205.251		205.252	
	N = 131	N = 76	Tio R 5 N = 88	Iprat 36 N = 89	PL N = 91	Tio R 5 N = 92	Iprat 36 N = 89	PL N = 90
Deaths, n (%)								
All-cause	2 (1.5)	2 (2.6)	0 (0)	0 (0)	0 (0)	1 (1.1)	1 (1.1)	0 (0)
CV-related	2 (1.5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.1)	0 (0)	0 (0)
COPD-related	0 (0)	2 (2.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.1)	0 (0)

COPD = chronic obstructive pulmonary disease; CV = cardiovascular; Iprat 36 = ipratropium 36 mcg 4 times daily; PL = placebo; Tio R 5 = Spiriva Respimat 5 mcg daily dose.
Notes: Study 205.249: n = 1 Tio R 5 due to cardiac arrest and n = 1 PL due to cardiorespiratory arrest.
Study 205.250: n = 1 Tio R 5 and n = 1 Tio H 18, both due to COPD exacerbations.
Study 205.251: n = 1 death due to COPD exacerbation in the Tio R 10 group.
Study 205.252: n = 1 Tio R 5 due to COPD exacerbation, delirium, gastrointestinal hemorrhage, and lung neoplasm, n = 1 Iprat 36 due to pancreatic carcinoma metastatic, and n = 1 death due to cardiac arrest/COPD exacerbation in the Tio R 10 group.
Source: Clinical Study Report (CSR) 205.249,[1] CSR 205.250,[2] CSR 205.251,[3] and CSR 205.252.[12]

TABLE 28: STUDIES 205.254, 205.255, AND 205.372 — ANALYSIS OF DEATHS BY TREATMENT (SAFETY SET)

Characteristic	Study					
	205.254		205.255		205.372[a]	
	Tio R 5 (N = 332)	PL (N = 319)	Tio R 5 (N = 338)	PL (N = 334)	Tio R 5 (N = 1,952)	PL (N = 1,965)
Deaths, n (%)						
All-cause	7 (2.1)	5 (1.6)	5 (1.5)	0 (0)	52 (2.7)	38 (1.9)
CV-related	1 (0.3)	0 (0)	1 (3.3)	0 (0)	9 (0.5)	4 (0.2)
COPD-related	1 (0.3)	0 (0)	1 (3.3)	0 (0)	0 (0)	0 (0)
Other	5 (1.5)	5 (1.6)	3 (0.9)	0 (0)	43 (2.2)	34 (1.7)

[a] Planned randomized treatment censored at day 337 (Treated set).
Notes: Study 205.254: n = 1 death due to cardiac failure and n = 1 death due to COPD exacerbation in the Tio R 5 group; n = 8 deaths in the Tio R 10 group, none were CV- or COPD-related.
Study 205.255: n = 1 death due to right ventricular failure and n = 1 death due to COPD exacerbation in the Tio R 5 group; n = 9 deaths in the Tio R 10 group, none were CV-related but n = 3 were COPD-related.
Source: Clinical Study Report (CSR) 205.254,[4] CSR 205.255,[5] and CSR 205.372.[13]

TABLE 29: STUDY 205.372 — ANALYSIS OF FATAL ADVERSE EVENTS (BY SYSTEM ORGAN CLASS) UP TO DAY 337 (SAFETY SET)

System Organ Class	Study				Rate Ratio (95% CI); *P* Value Tio R 5 vs. PL
	Tio R 5 (N = 1,952)		PL (N = 1,965)		
	No. of events	Incidence rate[b]	No. of events	Incidence rate[b]	
Patients with any fatal event,[a] N	52	2.94	38	2.13	1.38 (0.91 to 2.10); *P* = 0.1297
General disorders and administration site conditions	19	1.07	12	0.67	1.60 (0.78 to 3.29); *P* = 0.2037

System Organ Class	Study				Rate Ratio (95% CI); *P* Value Tio R 5 vs. PL
	Tio R 5 (N = 1,952)		PL (N = 1,965)		
	No. of events	Incidence rate[b]	No. of events	Incidence rate[b]	
Lower respiratory system disorders	9	0.51	16	0.89	0.57 (0.25 to 1.28); *P* = 0.1739
Cardiac disorders	9	0.51	4	0.22	2.27 (0.70 to 7.37); *P* = 0.1724
Infections and infestations	3	0.17	5	0.28	0.61 (0.14 to 2.53); *P* = 0.4919
Other respiratory system disorders[c]	5	0.28	2	0.11	2.52 (0.49 to 13.01); *P* = 0.2686
Neoplasms, benign, malignant and unspecified[d]	4	0.23	2	0.11	2.02 (0.37 to 11.02); *P* = 0.4176
Other organ classes with ≤ 2 events in total[e]	5	NR	2	NR	NR

CI = confidence interval; NR = not reported; PL = placebo; Tio R 5 = Spiriva Respimat 5 mcg daily dose.
[a] Adjudicated assignment to organ classes; number of events categorized by class exceeds number of patients in first table row because some deaths were due to 2 or more events in different classes.
[b] Per 100 patient-years.
[c] Comprising lung cancer (tiotropium, 5 events; placebo, 1 event) and pulmonary embolism (placebo, 1 event).
[d] Excluding lung cancer.
[e] Comprising gastrointestinal disorders (tiotropium, 1 event; placebo, 1 event); nervous system disorders (tiotropium, 1 event); psychiatric disorders (placebo, 1 event); renal and urinary disorders (tiotropium, 1 event), reproductive system disorders (tiotropium, 1 event) and upper respiratory system disorders (tiotropium, 1 event).
Source: Clinical Study Report 205.372,[13] Bateman et al., 2010.[37]

TABLE 30: STUDY 205.452 (TIOSPIR) — FREQUENCY [N (%)] OF PATIENTS WITH PRIMARY CAUSE OF DEATH AS DETERMINED BY ADJUDICATION BY TREATMENT AND PRIMARY SYSTEM ORGAN CLASS (DAS, INCLUDING VITAL STATUS FOLLOW-UP)

System Organ Class	Treatment, n (%)	
	Tio R 5 N = 5,711	Tio H 18 N = 5,694
Patients with primary cause of death determined by adjudication	423 (7.4)	439 (7.7)
Respiratory, thoracic, and mediastinal disorders	123 (2.2)	130 (2.3)
General disorders and administration site conditions	96 (1.7)	107 (1.9)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	100 (1.8)	95 (1.7)
Infections and infestations	34 (0.6)	34 (0.6)
Cardiac disorders	27 (0.5)	17 (0.3)
Gastrointestinal disorders	10 (0.2)	16 (0.3)
Injury, poisoning, and procedural complications	11 (0.2)	16 (0.3)
Nervous system disorders	16 (0.3)	13 (0.2)
Vascular disorders	3 (0.1)	5 (0.1)
Hepatobiliary disorders	1 (0.0)	2 (0.0)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)
Psychiatric disorders	2 (0.0)	4 (0.1)
Renal and urinary disorders	0 (0.0)	0 (0.0)

DAS = death analysis set; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; Tio R 5 = Spiriva Respimat 5 mcg daily dose.
Source: Clinical Study Report 205.452.[14]

TABLE 31: STUDY 205.452 (TIOSPIR) — ANALYSIS OF DEATHS BY TREATMENT (DAS, INCLUDING VITAL STATUS FOLLOW-UP)

Deaths	Treatment, n (%)	
	Tio R 5 N = 5,711	Tio H 18 N = 5,694
Patients with deaths	423 (7.4)	439 (7.7)
HR of events vs. Tio H 18 HR (95% CI)	0.957 (0.837 to 1.094)[a]	

CI = confidence interval; DAS = death analysis set; HR = hazard ratio; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; Tio R 5 = Spiriva Respimat 5 mcg daily dose.
[a] Non-inferiority between Tio R 5 and Tio H 18 was concluded if the upper limit of 95% CI for the HR was below 1.25, the pre-specified non-inferiority margin.
Source: Clinical Study Report 205.452.[14]

TABLE 32: STUDY 205.452 (TIOSPIR) — ANALYSIS OF FATAL ADVERSE EVENTS BY TREATMENT (DAS, ON-TREATMENT ONLY)

Fatal Adverse Events	Treatment, n (%)	
	Tio R 5 N = 5,711	Tio H 18 N = 5,694
Patients with fatal AEs	326 (5.7)	357 (6.3)
HR of events vs. Tio H 18 HR (95% CI)	0.913 (0.785 to 1.060)	

CI = confidence interval; DAS = death analysis set; HR = hazard ratio; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; Tio R 5 = Spiriva Respimat 5 mcg daily dose.
Source: Clinical Study Report 205.452.[14]

TABLE 33: STUDY 205.452 (TIOSPIR) — TIME AT RISK ADJUSTED RATES OF ADJUDICATED CAUSES OF DEATH WITH AN INCIDENCE RATE OF 0.1 OR GREATER IN ANY TREATMENT GROUP BY TREATMENT AT THE LEVEL OF SOC (DAS, INCLUDING VITAL STATUS FOLLOW-UP)

System Organ Class	Treatment				
	Tio R 5		Tio H 18		Tio R 5 vs. Tio H 18
	N	Rate	N	Rate	Rate Ratio (95% CI)
Number of patients	5,711		5,694		
Total treated with death events	423	3.2	439	3.4	0.96 (0.84 to 1.09)
Cardiac disorders	27	0.2	17	0.1	1.58 (0.86 to 2.89)
Gastrointestinal disorders	10	0.1	16	0.1	0.62 (0.28 to 1.37)
General disorders and administration site conditions	96	0.7	107	0.8	0.89 (0.68 to 1.17)
Infections and infestations	34	0.3	34	0.3	0.99 (0.62 to 1.60)
Injury, poisoning, and procedural complications	11	0.1	16	0.1	0.68 (0.32 to 1.47)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	100	0.8	95	0.7	1.05 (0.79 to 1.38)
Nervous system disorders	16	0.1	13	0.1	1.22 (0.59 to 2.54)
Respiratory, thoracic, and mediastinal disorders	123	0.9	130	1.0	0.94 (0.73 to 1.20)

CI = confidence interval; DAS = death analysis set; HR = hazard ratio; SOC = system organ class; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; Tio R 5 = Spiriva Respimat 5 mcg daily dose.
Notes: Patient-years at risk calculated from the start of treatment to the last known alive date.
Rate = Rate of first occurrence per 100 patient-years at risk.
Source: Clinical Study Report 205.452.[14]

TABLE 34: STUDIES 205.254 AND 205.255 — COPD EXACERBATIONS AND RELATED HOSPITALIZATIONS (POOLED ANALYSIS)

COPD Exacerbations and Hospitalizations	Treatment	
	Tio R 5 N = 670	PL N = 653
N (%) with ≥ 1 exacerbation	37.2	44.1
P value vs. PL	*P* < 0.01	
OR (95% CI)[a]	0.75 (0.60 to 0.93); *P* < 0.01	
Time (lower quartile) to first exacerbation (days)	160	86
P value vs. PL	*P* < 0.001	
COPD exacerbation rate (per patient-year)	0.93	1.91
Mean time (%) in exacerbation[b]	4.0	5.6
P value vs. PL	*P* < 0.01	
Mean hospitalization[c] per patient-year	0.12	0.20
Patients (%) with ≥ 1 hospitalization[c]	5.8	6.7

CI = confidence interval; COPD = chronic obstructive pulmonary disease; OR = odds ratio; PL = placebo; Tio R 5 = Spiriva Respimat 5 mcg daily dose.
[a] Compared with PL (chi-square, unadjusted for extent of exposure).
[b] Expressed as the mean of the percentage of days each patient remained on randomized treatment.
[c] Due to COPD exacerbations.
Source: Bateman E, et al. Int J Chron Obstruct Pulmon Dis. 2010;5:197-208.[15]

TABLE 35: STUDY 205.372 — SUMMARY OF COPD EXACERBATIONS BY SEVERITY AND TREATMENT (FAS)

COPD Exacerbations	Treatment , n (%)	
	Tio R 5	PL
Total number of exacerbations		
Any	1,168 (100.0)	1,434 (100.0)
Mild	317 (27.1)	379 (26.4)
Moderate	641 (54.9)	802 (55.9)
Severe	210 (18.0)	253 (17.6)
Total number of exacerbations and treatment		
Any	1,168 (100.0)	1,434 (100.0)
Antibiotics required	875 (74.9)	1,094 (76.3)
Oral or IV steroids required	601 (51.5)	759 (52.9)

COPD = chronic obstructive pulmonary disease; FAS = full-analysis set; IV = intravenous; PL = placebo; Tio R 5 = Spiriva Respimat 5 mcg daily dose.
Note: Period of risk from start of randomized treatment to the day after the last dose of randomized treatment.
Source: Clinical Study Report 205.372.[13]

TABLE 36: STUDY 205.372 — COX PROPORTIONAL HAZARDS ANALYSIS OF TIME TO FIRST COPD EXACERBATION (FAS)

COPD Exacerbations	Treatment	
	Tio R 5 N = 1,939	PL N = 1,953
N (%) with ≥ 1 exacerbation	685 (35.3)	842 (43.1)
N (%) of censored patients	1,254 (64.7)	1,111 (56.9)
HR[a] vs. PL (95% CI); *P* value[b]	0.693 (0.625 to 0.769); *P* < 0.0001	
N (%) with ≥ 1 moderate or severe exacerbation	538 (27.7)	666 (34.1)
N (%) of censored patients	1,401 (72.3)	1,287 (65.9)
HR[a] vs. PL (95% CI); *P* value[b]	0.699 (0.622 to 0.786); *P* < 0.0001	

CI = confidence interval; COPD = chronic obstructive pulmonary disease; FAS = full-analysis set; HR = hazard ratio; PL = placebo; Tio R 5 = Spiriva Respimat 5 mcg daily dose.
[a] Cox proportional hazards model included centre (pooled), long-acting beta-2 agonist use, and treatment as covariates.
[b] Wald chi-square test.
Note: Exacerbations were counted if they occurred between the date of the first dose of randomized treatment and the date of the last dose of randomized treatment plus 1 day (inclusive). Patients were censored at the end of the interval if no exacerbation had occurred.
Source: Clinical Study Report 205.372[13]

TABLE 37: STUDY 205.372 — COX PROPORTIONAL HAZARDS ANALYSIS OF TIME TO FIRST HOSPITALIZED COPD EXACERBATION (FAS)

COPD Exacerbations Leading to Hospitalization	Treatment	
	Tio R 5 N = 1,939	PL N = 1,953
N (%) with ≥ 1 exacerbation leading to hospitalization	161 (8.3)	198 (10.1)
N (%) of censored patients	1,778 (91.7)	1,755 (89.9)
HR[a] vs. PL (95% CI); *P* value[b]	0.728 (0.589 to 0.901); *P* = 0.0034	

CI = confidence interval; COPD = chronic obstructive pulmonary disease; FAS = full-analysis set; HR = hazard ratio; PL = placebo; Tio R 5 = Spiriva Respimat 5 mcg daily dose.
[a] Cox proportional hazards model included centre (pooled), LABA use, and treatment as covariates.
[b] Wald chi-square test.
Note: Exacerbations were counted if they occurred between the date of the first dose of randomized treatment and the date of the last dose of randomized treatment plus 1 day (inclusive). Patients were censored at the end of the interval if no exacerbation had occurred.
Source: Clinical Study Report 205.372.[13]

TABLE 38: STUDY 205.452 (TIOSPIR) — NUMBER OF COPD EXACERBATIONS (TS)

COPD Exacerbations	Treatment	
	Tio R 5	Tio H 18
Total number of COPD exacerbations	6,425	6,504
Total exposure (patient-years)	11,358	11,352
Observed number of events (per patient-year)	0.57	0.57
Adjusted rate of events (per patient-year) Mean (95% CI)	0.59 (0.56 to 0.61)	0.59 (0.57 to 0.61)
Rate ratio of events vs. Tio H 18 Mean (95% CI); *P* value[a]	0.99 (0.94 to 1.05); *P* = 0.8047	

CI = confidence interval; COPD = chronic obstructive pulmonary disease; PL = placebo; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; Tio R 5 = Spiriva Respimat 5 mcg daily dose; TS = treated set.
[a] Negative binomial regression.
Source: Clinical Study Report 205.452.[14]

TABLE 39: STUDY 205.452 (TIOSPIR) — ANALYSIS OF TIME TO FIRST COPD EXACERBATION BY TREATMENT (TS, ON-TREATMENT ONLY)

COPD Exacerbations	Treatment	
	Tio R 5 N = 5,705	Tio H 18 N = 5,687
Patients with COPD exacerbations, n (%)	2,733 (47.9)	2,782 (48.9)
Median time to event (95% CI) [days]	756 (692 to 816)	719 (672 to 777)
HR of events vs. Tio H 18 HR (95% CI); *P* value	0.978 (0.928 to 1.032); *P* = 0.4194	

CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; PL = placebo; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; Tio R 5 = Spiriva Respimat 5 mcg daily dose; TS = treated set.
Source: Clinical Study Report 205.452.[14]

TABLE 40: STUDY 205.452 — ANALYSIS OF TIME TO FIRST MODERATE-TO-SEVERE COPD EXACERBATION BY TREATMENT (TS, ON-TREATMENT ONLY)

COPD Exacerbations	Treatment	
	Tio R 5 N = 5,705	Tio H 18 N = 5,687
Patients with moderate-to-severe COPD exacerbations, n (%)	2,694 (47.2)	2,732 (48.0)
HR of events vs. Tio H 18 HR (95% CI); *P* value	0.983 (0.932 to 1.037); *P* = 0.5377	

CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; PL = placebo; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; Tio R 5 = Spiriva Respimat 5 mcg daily dose; TS = treated set.
Source: Clinical Study Report 205.452.[14]

TABLE 41: STUDY 205.452 (TIOSPIR) — NUMBER OF MODERATE-TO-SEVERE COPD EXACERBATIONS (TS, ON-TREATMENT ONLY)

COPD Exacerbations	Treatment	
	Tio R 5 N = 5,705	Tio H 18 N = 5,687
Total number of moderate-to-severe COPD exacerbations	6,308	6,362
Total exposure (patient-year)	11,358	11,352
Observed number of events (per patient-year)	0.56	0.56
Adjusted rate of events (per patient-year)[a] Mean (95% CI)	0.58 (0.55 to 0.60)	0.58 (0.55 to 0.60)
Rate ratio of events vs. Tio H 18 Mean (95% CI); *P* value[b]	1.00 (0.94 to 1.06); *P* = 0.9242	

CI = confidence interval; COPD = chronic obstructive pulmonary disease; PL = placebo; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; Tio R 5 = Spiriva Respimat 5 mcg daily dose; TS = treated set.
[a] Model includes the fixed, categorical effects of treatment, investigative site, visit, and treatment-by-visit interaction, and continuous, fixed covariates of baseline and baseline-by-visit interaction, and a random term of patient.
[b] Binomial regression.
Source: Clinical Study Report 205.452.[14]

TABLE 42: STUDY 205.452 — ANALYSIS OF TIME TO FIRST COPD EXACERBATIONS ASSOCIATED WITH HOSPITALIZATION BY TREATMENT (TS, ON-TREATMENT ONLY)

COPD Exacerbations	Treatment	
	Tio R 5 N = 5,705	Tio H 18 N = 5,687
Patients with hospitalizations due to COPD exacerbations, N (%)	826 (14.5)	811 (14.3)
HR of events vs. Tio H 18 HR (95% CI); *P* value	1.024 (0.929 to 1.128); *P* = 0.6384	

CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; PL = placebo; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; Tio R 5 = Spiriva Respimat 5 mcg daily dose; TS = treated set.
Source: Clinical Study Report 205.452[14]

TABLE 43: STUDY 205.452 (TIOSPIR) — NUMBER OF COPD EXACERBATIONS ASSOCIATED WITH HOSPITALIZATION (TS)

COPD Exacerbations	Treatment	
	Tio R 5 N = 5,705	Tio H 18 N = 5,687
Total number of hospitalizations due to COPD exacerbations	1,284	1,216
Total exposure (patient−year)	11,358	11,352
Observed number of events (per patient−year)	0.11	0.11
Adjusted rate of events (per patient−year)[a] Mean (95% CI)	0.12 (0.11 to 0.13)	0.11 (0.10 to 0.12)
Rate ratio of events vs. Tio H 18 Mean (95% CI); *P* value[a]	1.06 (0.94 to 1.18); *P* = 0.3441	

CI = confidence interval; COPD = chronic obstructive pulmonary disease; PL = placebo; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; Tio R 5 = Spiriva Respimat 5 mcg daily dose; TS = treated set.
[a] Negative binomial regression.
Source: Clinical Study Report 205.452.[14]

TABLE 44: STUDIES 205.254, 205.255, AND 205.372 — ST GEORGE'S RESPIRATORY QUESTIONNAIRE SCORES AT DAY 337 (FAS)[B]

	Study					
	205.254		205.255		205.372	
	Tio R 5 N = 318	PL N = 275	Tio R 5 N = 324	PL N = 307	Tio R 5 N = 1,690	PL N = 1,668
Baseline, Mean[a]						
Symptoms	51.755		50.100		46.8 (23.7)	48.7 (23.1)
Activities	59.480		61.136		58.4 (20.8)	59.3 (20.9)
Impacts	34.430		33.594		33.8 (20.2)	35.2 (20.5)
Total	44.930		44.719		43.5 (18.2)	44.8 (18.3)
Day 337, Mean[b] (SE)						
Symptoms	42.323 (1.064)	47.835 (1.146)	40.680 (1.116)	48.244 (1.185)	40.069 (0.541)	44.009 (0.542)
Activities	56.317 (0.823)	58.629 (0.887)	58.529 (0.897)	60.921 (0.953)	55.173 (0.451)	58.168 (0.453)
Impacts	29.413 (0.743)	32.466 (0.801)	28.858 (0.783)	32.239 (0.832)	29.029 (0.404)	31.932 (0.405)
Total	39.648 (0.676)	42.917 (0.728)	39.771 (0.718)	43.484 (0.763)	38.874 (0.367)	41.841 (0.368)

	Study					
	205.254		205.255		205.372	
	Tio R 5 N = 318	PL N = 275	Tio R 5 N = 324	PL N = 307	Tio R 5 N = 1,690	PL N = 1,668
Txt Diff at Day 337, Mean (95% CI); *P* value						
Symptoms	–5.512 (–8.589 to –2.435); *P* = 0.0005		–7.565 (–10.771 to –4.359); *P* < 0.0001		–4.0 (–5.3 to –2.6); *P* < 0.0001	
Activities	–2.311 (–4.691 to 0.068); *P* = 0.0569		–2.393 (–4.972 to 0.186); *P* = 0.0690		–3.0 (–4.1 to –1.8); *P* < 0.0001	
Impacts	–3.053 (–5.202 to –0.904); *P* = 0.0054		–3.380 (–5.630 to –1.130); *P* = 0.0033		–2.8 (–3.8 to –1.8); *P* < 0.0001	
Total	–3.269 (–5.224 to –1.315): *P* = 0.0011		–3.713 (–5.778 to –1.647); *P* = 0.0004		–2.9 (–3.9 to –2.0); *P* < 0.0001	

CI = confidence interval; FAS = full-analysis set; LABA = long-acting beta-2 agonist; PL = placebo; QoL = quality of life; SE = standard error; Tio R 5 = Spiriva Respimat 5 mcg daily dose; Txt Diff = treatment difference.
[a] Common unadjusted baseline mean.
[b] Studies 205.254 and 205.255 are FAS-QoL (FAS definition); Study 205.372 is FAS.
Notes: Study 205.254 and 205.255 means adjusted for centre, smoking status at entry, and baseline values; Study 205.372 means adjusted for baseline, pooled centre, and LABA use at randomization.
Source: Clinical Study Report 205.254,[4] Clinical Study Report 205.255,[5] and Clinical Study Report 205.372.[13]

TABLE 45: STUDIES 205.249 AND 205.250 — TROUGH FEV_1 (L) RESPONSE AFTER 4-WEEK TREATMENT PERIODS (FAS-PEP)

	Study					
	205.249			205.250		
	Tio R 5 N = 112	Tio H 18 N = 112	PL N = 108	Tio R 5 N = 75	Tio H 18 N = 75	PL N = 76
Baseline FEV_1 (L)						
Mean (SD)	1.011 (0.392)			1.121 (0.362)		
Day 29 FEV_1 Response (L)						
Mean (SE)	0.093 (0.013)	0.048 (0.013)	–0.023 (0.013)	0.056 (0.014)	0.055 (0.014)	–0.070 (0.014)
Txt Diff in FEV_1 Response on Day 29, Mean (95% CI); *P* Value[a]						
Tio R 5 vs. PL	0.116 (0.083 to 0.149); *P* < 0.001 (Superiority)			0.126 (0.086 to 0.166); *P* < 0.001 (Superiority)		
Tio R 5 vs. Tio H 18	0.045 (0.013 to 0.078); *P* < 0.001 (Non-inferiority)[b]			0.001 (–0.039 to 0.041); *P* = 0.006 (Non-inferiority)[b]		
Tio H vs. PL	0.070 (0.037 to 0.104); *P* < 0.001 (Superiority)			0.125 (0.085 to 0.165); *P* < 0.001 (Superiority)		

CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; PL = placebo; SD = standard deviation; SE = standard error; Tio H 18 = Spiriva HandiHaler 18 mcg daily; Tio R 5 = Spiriva Respimat 5 mcg daily dose; vs = versus.
[a] *P* values are one-sided.
[b] Non-inferiority was concluded if at a (one-sided) *P* < 0.025, the lower bound of the 95% CI for the absolute difference in trough FEV_1 was above –0.50 L, the pre-specified non-inferiority margin.
Note: Study 205.249 and 205.250 means are adjusted for centre, patient (within centre), period and baseline FEV_1.
Source: Clinical Study Reports 205.249[1] and 205.250.[2]

TABLE 46: STUDIES 205.251 AND 205.252 — TROUGH FEV_1 (L) RESPONSE AT END OF 12 WEEKS (FAS)

	Study					
	205.251			205.252		
	Tio R 5 N = 85	Iprat 36 N = 84	PL N = 87	Tio R 5 N = 90	Iprat 36 N = 86	PL N = 84
Baseline						
Mean (SD)	1.146 (0.367)	1.248 (0.401)	1.244 (0.395)	0.995 (0.417)	0.957 (0.409)	1.130 (0.426)
Day 85						
Mean (SE)	1.337 (0.026)	1.288 (0.026)	1.229 (0.026)	1.109 (0.020)	1.029 (0.020)	0.985 (0.021)
Txt Diff in FEV_1 response on Day 85, Mean (95% CI); *P* value						
Tio R 5 vs. PL	0.109 (0.036 to 0.181); $P = 0.0034$[a] (Superiority)			0.124 (0.067 to 0.181); $P < 0.0001$[a] (Superiority)		
Tio R 5 vs. Iprat 36	0.049 (–0.024 to 0.122); $P = 0.0041$[b,c] (Non-inferiority); $P = 0.1897$[a] (Superiority)			0.080 (0.024 to 0.136); $P < 0.0001$[b, c] (Non-inferiority); $P = 0.0055$ (Superiority)		
Iprat 36 vs. PL	0.060 (SE = 0.037[d]); $P = 0.1045$[a] (Superiority)			0.044 (SE = 0.029[d]); $P = 0.1373$[a] (Superiority)		

CI = confidence interval; FAS = full-analysis set; FEV_1 = forced expiratory volume in 1 second; Iprat 36 = Ipratropium 36 mcg 4 times daily dose; L = litre; PL = placebo; SD = standard deviation; SE = standard error; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; Tio R 5 = Spiriva Respimat 5 mcg daily dose; Txt Diff = treatment difference.

[a] *P* values are two-sided.

[b] *P* values are one-sided.

[c] Non-inferiority was concluded if at a (one-sided) $P < 0.025$, the lower bound of the 95% CI for the absolute difference in trough FEV_1 was above –0.50 L, the pre-specified non-inferiority margin.

[d] Only SE (no 95% CIs) was reported in the clinical study report for the comparison between Iprat 36 and PL.

Note: Study 205.251 and 205.252 baseline values are unadjusted means at –10 minutes pre-dose of study drug and day 85 values are adjusted means for centre, smoking status at entry, and baseline value.

Source: Clinical Study Reports 205.251[3] and 205.252.[12]

TABLE 47: STUDIES 205.254, 205.255, AND 205.372 — TROUGH FEV_1 (L) RESPONSE AT DAY 337 (FAS)[c]

	Study					
	205.254		205.255		205.372	
	Tio R 5 N = 326	PL N = 296	Tio R 5 N = 324	PL N = 307	Tio R 5 N = 1,889	PL N = 1,870
Baseline, Mean (SD or SE)[a]	1.049 (0.370)	1.085 (0.373)	1.087 (0.420)	1.049 (0.40)	1.111 (0.009)	1.106 (0.009)
Day 337, Mean (SE)	1.173 (0.013)	1.031 (0.014)	1.137 (0.012)	1.024 (0.012)	1.228 (0.007)	1.126 (0.007)
Txt Diff at Day 337, Mean (95% CI); *P* Value[b]	0.142 (0.104 to 0.181); $P < 0.0001$		0.113 (0.078 to 0.147); $P < 0.0001$		0.102 (0.085 to 0.118); $P < 0.0001$	

CI = confidence interval; FAS = full-analysis set; FEV_1 = forced expiratory volume in 1 second; LABA = long-acting beta-2 agonist; PL = placebo; SD = standard deviation; SE = standard error; Tio R 5 = Spiriva Respimat 5 mcg daily dose; Txt Diff = treatment difference.

[a] Studies 205.254 and 205.255 is SD and Study 205.372 is SE.

[b] Based on two-sided test.

[c] Studies 205.254 and 205.255 is FAS-PFT (FAS clinic spirometry); Study 205.372 is FAS.

Note: Study 205.254 and 205.255 means adjusted for treatment, smoking status at entry, centre and baseline values; Study 205.372 means adjusted for baseline, pooled centre, and LABA use at randomization.

Source: Clinical Study Report (CSR) 205.254,[4] CSR 205.255,[5] and CSR 205.372.[13]

TABLE 48: STUDY 205.452 (TIOSPIR) — TROUGH FEV_1 (L) COMPARISON OVER ON-TREATMENT VISITS THROUGH 120 WEEKS (TREATMENT MAIN EFFECTS) (SSS)

	MMRM Comparison Versus Tio H 18					
Treatment	N	Adjusted[a] Mean (L)	SE	Adjusted Mean of Difference (L)	SE	95% CI
Tio R 5	461	1.285	0.012	–0.010	0.014	(–0.038 to 0.018)[b]
Tio H 18	445	1.295	0.012			

CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; MMRM = mixed-model repeated measures; SE = standard error; SSS = spirometry sub-study; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; Tio R 5 = Spiriva Respimat 5 mcg daily dose; Txt Diff = treatment difference.

[a] Model includes the fixed, categorical effects of treatment, investigative site, visit, and treatment-by-visit interaction, and continuous, fixed covariates of baseline and baseline-by-visit interaction, and a random term of patient.

[b] Non-inferiority was achieved if the lower bound of the 95% CI for the absolute difference in trough FEV_1 was above –0.50 L, the pre-specified non-inferiority margin.

Source: Clinical Study Report 205.452.[14]

TABLE 49: STUDIES 205.251 AND 205.252 — COPD SYMPTOM SCORES AT 12 WEEKS (FAS)

COPD Symptoms	Study					
	205.251			205.252		
	Tio R 5 N = 85	Iprat 36 N = 84	PL N = 87	Tio R 5 N = 92	Iprat 36 N = 89	PL N = 90
Baseline Mean[a]						
Wheezing	0.8			0.8		
Shortness of breath	1.6			1.6		
Coughing	1.1			1.0		
Tightness of chest	0.6			0.5		
Day 85 Txt Diff (SE); *P* value						
Tio R 5 vs. PL						
Wheezing	–0.1 (0.1); *P* = 0.4414			–0.3 (0.1); *P* = 0.0156		
Shortness of breath	–0.1 (0.1); *P* = 0.3966			0.0 (0.1); *P* = 0.6631		
Coughing	–0.1 (0.1); *P* = 0.4128			–0.1 (0.1); *P* = 0.2222		
Tightness of chest	–0.3 (0.1); *P* = 0.0039			–0.1 (0.1); *P* = 0.1713		
Tio R 5 vs. Iprat 36						
Wheezing	–0.1 (0.1); *P* = 0.2119			–0.1 (0.1); *P* = 0.3860		
Shortness of breath	–0.2 (0.1); *P* = 0.0400			0.1 (0.1); *P* = 0.6201		
Coughing	–0.1 (0.1); *P* = 0.5633			0.1 (0.1); *P* = 0.2006		
Tightness of chest	–0.4 (0.1); *P* = 0.0005			–0.1 (0.1); *P* = 0.4587		
Iprat 36 vs. PL						
Wheezing	0.0 (0.1); *P* = 0.6234			–0.2 (0.1); *P* = 0.1227		
Shortness of breath	0.1 (0.1); *P* = 0.2213			–0.0 (0.1); *P* = 0.9542		
Coughing	–0.0 (0.1); *P* = 0.8154			–0.3 (0.1); *P* = 0.0136		
Tightness of chest	0.1 (0.1); *P* = 0.5358			–0.1 (0.1); *P* = 0.5301		

ANCOVA = analysis of covariance; COPD = chronic obstructive pulmonary disease; FAS = full-analysis set; Iprat 36 = ipratropium 36 mcg four times daily dose; PL = placebo; SE = standard error; Tio R 5 = Spiriva Respimat 5 mcg daily dose; Txt Diff = treatment difference.

[a] Common baseline mean.

Notes: Based on an ANCOVA analysis with means adjusted for centre, smoking status at entry, and baseline value.
Scale: 0 = None, 1 = Mild, 2 = Moderate, 3 = Severe symptoms.

Source: Clinical Study Reports 205.251[3] and 205.252.[12]

TABLE 50: STUDIES 205.254 AND 205.255 — COPD SYMPTOM SCORES AT DAY 337 (FAS-SYM)

COPD Symptoms	Study			
	205.254		205.255	
	Tio R 5 N = 326	PL N = 295	Tio R 5 N = 325	PL N = 304
Baseline, Mean[a]				
Wheezing	0.87		0.77	
Shortness of Breath	1.66		1.67	
Coughing	1.20		1.10	
Tightness of Chest	0.80		0.68	
Day 337, Mean (SE)				
Wheezing	0.67 (0.04)	0.91 (0.04)	0.66 (0.04)	0.85 (0.04)
Shortness of Breath	1.35 (0.04)	1.51 (0.04)	1.42 (0.04)	1.61 (0.04)
Coughing	1.05 (0.04)	1.21 (0.04)	0.96 (0.04)	1.06 (0.04)
Tightness of Chest	0.61 (0.04)	0.78 (0.04)	0.51 (0.04)	0.64 (0.04)
Txt Diff at Day 337, Mean (SE); *P* value				
Wheezing	–0.24 (0.05); $P < 0.0001$		–0.19 (0.05); $P = 0.0003$	
Shortness of Breath	–0.16 (0.05); $P = 0.0027$		–0.19 (0.05); $P = 0.0006$	
Coughing	–0.16 (0.06); $P = 0.0037$		–0.10 (0.06); $P = 0.0773$	
Tightness of Chest	–0.16 (0.05); $P = 0.0014$		–0.13 (0.05); $P = 0.0107$	

COPD = chronic obstructive pulmonary disease; FAS-SYM = full-analysis set – symptoms; PL = placebo; SE = standard error; Tio R 5 = Spiriva Respimat 5 mcg daily dose; Txt Diff = treatment difference.
[a] Common unadjusted baseline mean.
Notes: Studies 205.254 and 205.255 means adjusted for treatment, smoking status at entry, centre and baseline values.
Scale: 0 = None, 1 = Mild, 2 = Moderate, 3 = Severe symptoms.
Source: Clinical Study Reports 205.254[4] and 205.255.[5]

TABLE 51: STUDIES 205.254 AND 205.255 — MAHLER TDI SCORES AT DAY 337 (FAS-TDI)

TDI Score	Study			
	Study 205.254		Study 205.255	
	Tio R 5 N = 318	PL N = 273	Tio R 5 N = 324	PL N = 307
Baseline, Mean[a]				
Functional impairment	2.272		2.243	
Magnitude of tasks	2.196		2.111	
Magnitude of effort	2.023		1.972	
Focal score	6.491		6.326	
Day 337, Mean (SE)				
Functional impairment	0.606 (0.049)	0.255 (0.053)	0.630 (0.057)	0.318 (0.060)
Magnitude of tasks	0.650 (0.052)	0.291 (0.056)	0.654 (0.057)	0.275 (0.060)
Magnitude of effort	0.633 (0.056)	0.240 (0.060)	0.604 (0.061)	0.264 (0.065)
Focal score	1.895 (0.151)	0.791 (0.163)	1.880 (0.167)	0.869 (0.177)

TDI Score	Study			
	Study 205.254		Study 205.255	
	Tio R 5 N = 318	PL N = 273	Tio R 5 N = 324	PL N = 307
Txt Diff at Day 337, Mean (95% CI); *P* Value				
Functional impairment	0.351 (0.208 to 0.494); *P* < 0.0001		0.312 (0.149 to 0.475); *P* = 0.0002	
Magnitude of tasks	0.359 (0.209 to 0.510); *P* < 0.0001		0.380 (0.218 to 0.542); *P* < 0.0001	
Magnitude of effort	0.393 (0.231 to 0.555); *P* < 0.0001		0.340 (0.164 to 0.516); *P* = 0.0002	
Focal score	1.104 (0.667 to 1.540); *P* < 0.0001		1.011 (0.531 to 1.490); *P* < 0.0001	

CI = confidence interval; FAS-TDI = full-analysis set – Transition Dyspnea Index; PL = placebo; SE = standard error; TDI = Transition Dyspnea Index; Tio R 5 = Spiriva Respimat 5 mcg daily dose; Txt Diff = treatment difference.
[a] Common unadjusted baseline mean.
Notes: Study 205.254 and 205.255 means adjusted for treatment, smoking status at entry, centre and baseline values. Grades: −3 = Major deterioration, −2 = Moderate deterioration, −1 = Minor deterioration, 0 = No change, 1 = Minor improvement, 2 = Moderate improvement, 3 = Major improvement; focal score is the sum of components.
Source: Clinical Study Reports 205.254[4] and 205.255.[5]

TABLE 52: STUDIES 205.249 AND 205.250 — RESCUE MEDICATION USE (DAILY NUMBER OF OCCASIONS) (FAS)

	Study					
	205.249			205.250		
	Tio R 5 N = 110	Tio H 18 N = 111	PL N = 100	Tio R 5 N = 75	Tio H 18 N = 75	PL N = 76
Daytime Rescue Medication Use						
Baseline mean	2.90	2.86	3.04	1.40	1.38	1.45
Overall, mean (SE)	2.27 (0.10)	2.48 (0.10)	3.16 (0.11)	1.55 (0.09)	1.50 (0.09)	2.33 (0.09)
Nighttime Rescue Medication Use						
Baseline mean	0.54	0.51	0.54	0.39	0.42	0.42
Overall, mean (SE)	0.45 (0.05)	0.51 (0.05)	0.69 (0.05)	0.45 (0.04)	0.45 (0.04)	0.78 (0.04)
24-hour Rescue Medication Use						
Baseline mean	3.43	3.37	3.58	1.79	1.80	1.87
Overall, mean (SE)	2.73 (0.13)	2.99 (0.13)	3.84 (0.14)	2.00 (0.12)	1.95 (0.12)	3.11 (0.12)

FAS = full-analysis set; FEV_1 = forced expiration volume in 1 second; PL = placebo; SE = standard error; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; Tio R 5 = Spiriva Respimat 5 mcg daily dose.
Note: Means are adjusted for centre, patient (within centre), period and baseline FEV_1.
Source: Clinical Study Report 205.249[1] and Clinical Study Report 205.250.[2]

TABLE 53: STUDIES 205.251 AND 205.252 — WEEKLY MEAN NUMBER OF OCCASIONS OF RESCUE SALBUTAMOL USE PER 24 HOURS (FAS-DRY)

Rescue Salbutamol Use	Study					
	205.251			205.252		
	Tio R 5 N = 85	Iprat 36 N = 83	PL N = 87	Tio R 5 N = 89	Iprat 36 N = 85	PL N = 83
Baseline mean[a]	2.9			2.6		
Week 12, mean (SE)	2.5 (0.2)	2.7 (0.2)	2.8 (0.2)	2.1 (0.2)	2.3 (0.2)	2.7 (0.2)
Week 12 Txt Diff (SE); *P* Value						
Tio R 5 vs. PL	–0.2 (0.3); *P* = 0.4735			–0.6 (0.3); *P* = 0.0209		
Tio R 5 vs. Iprat 36	–0.1 (0.3); *P* = 0.7015			–0.2 (0.3); *P* = 0.5364		
Iprat 36 vs. PL	–0.1 (0.3); *P* = 0.7435			–0.4 (0.3); *P* = 0.0948		

ANCOVA = analysis of covariance; FAS-DRY = full-analysis set — diary; Iprat 36 = ipratropium 36 mcg four times daily; PL = placebo; SE = standard error; Tio R 5 = Spiriva Respimat 5 mcg daily dose; Txt Diff = treatment difference.
[a] Common baseline mean; based on ANCOVA analysis with terms for treatment, smoking status at entry, centre and baseline value.
Source: Clinical Study Reports 205.251[3] and 205.252.[12]

TABLE 54: STUDIES 205.254 AND 205.255 — WEEKLY MEAN NUMBER OF OCCASIONS OF RESCUE SALBUTAMOL USED PER 24 HOURS (FAS-DRY)

Rescue Salbutamol Use	Study			
	205.254		205.255	
	Tio R 5 N = 324	PL N = 293	Tio R 5 N = 321	PL N = 311
Baseline mean[a]	2.5		2.7	
Week 48, mean (SE)	2.3 (0.1)	3.1 (0.1)	2.8 (0.1)	3.2 (0.1)
Week 48 Txt Diff (SE); *P* value				
Tio R 5 vs. PL	–0.8 (0.2); *P* < 0.0001		–0.4 (0.2); *P* = 0.0169	

FAS-DRY = full-analysis set – diary; PL = placebo; SE = standard error; Tio R 5 = Spiriva Respimat 5 mcg daily dose; Txt Diff = treatment difference.
[a] Common baseline mean.
Note: Means adjusted for centre, smoking status at entry and baseline value.
Source: Clinical Study Reports 205.254[4] and 205.255.[5]

TABLE 55: STUDIES 205.249 AND 205.250 — COMPLIANCE TO STUDY MEDICATION (SAFETY SET)

Characteristic	Study					
	205.249			205.250		
	Tio R 5 N = 112	Tio H 18 N = 112	PL N = 108	Tio R 5 N = 75	Tio H 18 N = 75	PL N = 76
No. of complete doses inhaled						
N	111	112	103	75	75	76
Mean (SD)	28.5 (4.1)	28.6 (5.6)	26.2 (7.5)	27.7 (3.7)	28.2 (2.4)	28.3 (2.7)
Median	27.0	27.0	27.0	27.0	27.0	28.0
Range	18 to 48	3 to 53	1 to 43	2 to 32	23 to 37	19 to 35
Compliance (%)						
Missing						
N	111	112	102	75	75	76
Mean (SD)	98.7 (4.5)	98.8 (4.5)	99.1 (2.3)	100.0 (0.4)	99.9 (0.6)	99.6 (3.5)
Median	100.0	100.0	100.0	100.0	100.0	100.0
Range	58 to 100	67 to 103	90 to 100	96 to 100	96 to 100	70 to 100

Characteristic	Study					
	205.249			205.250		
	Tio R 5 N = 112	Tio H 18 N = 112	PL N = 108	Tio R 5 N = 75	Tio H 18 N = 75	PL N = 76
Compliance (% of complete doses inhaled), n (%)						
< 80%	1 (0.9)	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
80% to 100%	110 (98.2)	109 (97.3)	102 (94.4)	75 (100.0)	75 (100.0)	75 (98.7)
> 100%	0 (0.0)	1 (0.9)	0 (0.0)	NA	NA	NA
Missing	1 (0.9)	0 (0.0)	6 (5.6)	NA	NA	NA

PL = placebo; SD = standard deviation; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; Tio R 5 = Spiriva Respimat 5 mcg daily dose.
Note: Compliance was calculated based on the entries in the daily diary card as the percentage of complete doses inhaled divided by the duration of treatment. Data related to visit-days were not used for calculation.
Source: Clinical Study Reports 205.249[1] and 205.250.[2]

TABLE 56: STUDIES 205.251 AND 205.252 — COMPLIANCE TO STUDY MEDICATION BY DEVICE (SAFETY SET)

Characteristic	Study					
	205.251			205.252		
	Tio R 5 N = 88	Iprat 36 N = 89	PL N = 91	Tio R 5 N = 92	Iprat 36 N = 89	PL N = 90
Respimat Device Only						
Medication taken (% of prescribed)						
N	88	88	89	92	88	89
Mean (SD)	97.9 (6.7)	98.2 (5.6)	97.9 (6.4)	98.0 (6.2)	98.3 (7.2)	97.7 (10.3)
Median	100.0	100.0	100.0	100.0	100.0	100.0
Range	63.6 to 100	52.2 to 100	59.3 to 100	57.3 to 100	47.1 to 100	6.9 to 100
Medication taken (% of prescribed), n (%)						
Missing	0 (0	1 (1.1)	2 (2.2)	0 (0.0)	1 (1.1)	1 (1.1)
< 60	0 (0)	1 (1.1)	1 (1.1)	1 (1.1)	2 (2.2)	1 (1.1)
60 to 80	4 (4.5)	0 (0)	2 (2.2)	1 (1.1)	0 (0.0)	1 (1.1)
80 to 100	84 (95.5)	87 (97.8)	86 (94.5)	90 (97.8)	86 (96.6)	87 (96.7)
MDI Device Only						
Medication taken (% of prescribed)						
N	88	88	89	92	88	89
Mean (SD)	95.8 (9.5)	96.0 (12.0)	96.4 (7.2)	95.9 (7.7)	96.6 (8.4)	96.9 (6.0)
Median	99.1	98.8	98.8	98.5	98.8	98.8
Range	37.5 to 100	0 to 100	62.5 to 100	53.4 to 100	38.2 to 100	58.8 to 100
Medication taken (% of prescribed), n (%)						
Missing	0 (0)	1 (1.1)	2 (2.2)	0 (0.0)	1 (1.1)	1 (1.1)
< 60	1 (1.1)	2 (2.2)	0 (0)	2 (2.2)	2 (2.2)	1 (1.1)
60 to 80	4 (4.5)	0 (0)	3 (3.3)	2 (2.2)	1 (1.1)	2 (2.2)
80 to 100	83 (94.3)	86 (96.6)	86 (94.5)	88 (95.7)	85 (95.5)	86 (95.6)

Iprat 36 = ipratropium 36 mcg four times daily; PL = placebo; SD = standard deviation; Tio R 5 = Spiriva Respimat 5 mcg daily dose.
Source: Clinical Study Reports 205.251[3] and 205.252.[12]

TABLE 57: STUDIES 205.254 AND 205.255 — COMPLIANCE WITH STUDY MEDICATION (SAFETY SET)

Characteristic	Study			
	205.254		205.255	
	Tio R 5 N = 332	PL N = 319	Tio R 5 N = 338	PL N = 334
Medication taken (% of prescribed)				
N	328	308	334	329
Mean (SD)	96.9 (9.4)	95.5 (13.1)	95.3 (13.1)	96.0 (10.0)
Median	99.7	99.7	99.4	99.6
Range	7.7 to 100	6.7 to 100	0 to 100	18.6 to 100
Medication taken (% of prescribed), n (%)				
Missing	4 (1.2)	11 (3.4)	4 (1.2)	5 (1.5)
< 60	6 (1.8)	9 (2.8)	12 (3.6)	6 (1.8)
60 to 80	6 (1.8)	11 (3.4)	12 (3.6)	11 (3.3)
> 80 to 100	316 (95.2)	288 (90.3)	310 (91.7)	312 (93.4)

PL = placebo; SD = standard deviation; Tio R 5 = Spiriva Respimat 5 mcg daily dose.
Source: Clinical Study Reports 205.254[4] and 205.255.[5]

TABLE 58: STUDY 205.372 — MEDICATION COMPLIANCE BY CATEGORIES (TS)

Characteristic	Treatment	
	Tio R 5 N = 1,952	PL N = 1,962
Medication Taken (% of prescribed), n (%)		
< 50	62 (3.2)	87 (4.4)
50 to < 80	185 (9.5)	215 (10.9)
80 to < 120	1,641 (84.1)	1,603 (81.6)
120 to 200	27 (1.4)	27 (1.4)
> 200	1 (0.1)	0 (0.0)
Missing	36 (1.8)	33 (1.7)

PL = placebo; Tio R 5 = Spiriva Respimat 5 mcg daily dose; TS = treated set.
Source: Clinical Study Report 205.372.[13]

TABLE 59: STUDY 205.452 (TIOSPIR) — ADHERENCE TO STUDY MEDICATION BY DEVICE (TS)

Characteristic	Study	
	Tio R 5 N = 5,705	Tio H 18 N = 5,687
RESPIMAT Device Only		
Prescribed study medication administered (%)		
N	5,385	5,381
Mean (SD)	96.0 (11.2)	96.2 (9.0)
Median	97.6	97.7
Missing	320	306
Medication taken (% of prescribed), n (%)		
< 80%	219 (3.8)	182 (3.2)
80% to 120%	5,139 (90.1)	5,174 (91.0)
≥ 120%	27 (0.5)	25 (0.4)
Missing	320 (5.6)	306 (5.4)

Characteristic	Study	
	Tio R 5 N = 5,705	Tio H 18 N = 5,687
HandiHaler Device Only		
Prescribed study medication administered (%)		
N	5,385	5,383
Mean (SD)	97.2 (10.2)	97.5 (8.8)
Median	99.0	99.0
Missing	320	304
Medication taken (% of prescribed), n (%)		
< 80%	179 (3.1)	145 (2.5)
80% to 120%	5,183 (90.9)	5,207 (91.6)
≥ 120%	23 (0.4)	31 (0.5)
Missing	320 (5.6)	304 (5.3)

SD = standard deviation; Tio H 18 = Spiriva HandiHaler 18 mcg daily dose; Tio R 5 = Spiriva Respimat 5 mcg daily dose; TS = treated set.
Source: Clinical Study Report 205.452.[14]

TABLE 60: STUDY 205.252 — SUMMARY OF PATIENT SATISFACTION WITH INHALER ATTRIBUTES (SAFETY SET)

Attribute	Treatment					
		Tio R 5		Iprat 36		PL
	N	Diff. (Resp.- MDI), Mean (SE); *P* Value	N	Diff. (Resp. – MDI), Mean (SE); *P* Value	N	Diff. (Resp. – MDI), Mean (SE); *P* Value
Performance and Reliability						
Satisfied with overall feeling of inhaling the medicine?	52	–0.2 (0.2); *P* = 0.2933	47	–0.4 (0.3); *P* = 0.1112	49	–0.0 (0.2); *P* = 0.9287
Satisfied with the feeling that the inhaled dose goes to the lungs?	52	–0.2 (0.2); *P* = 0.3138	47	–0.6 (0.2); *P* = 0.0275	49	0.1 (0.2); *P* = 0.4874
Satisfied that you can tell the amount of medicine left in the container?	50	0.9 (0.3); *P* = 0.0023	47	0.7 (0.3); *P* = 0.0288	47	0.9 (0.3); *P* = 0.0019
Satisfied that the inhaler works reliably?	52	–0.0 (0.1); *P* = 0.7885	47	–0.3 (0.2); *P* = 0.1001	49	0.2 (0.1); *P* = 0.0898
Satisfied with the ease of inhaling a dose?	51	0.0 (0.2); *P* = 0.8406	47	–0.4 (0.2); *P* = 0.0510	49	0.1 (0.2); *P* = 0.5058
Satisfied with using the inhaler?	52	–0.0 (0.2); *P* = 0.8422	47	–0.4 (0.2); *P* = 0.0516	49	0.0 (0.1); *P* = 0.7847
Satisfied with medication speed coming out of the inhaler?	53	0.0 (0.2); *P* = 0.8695	47	–0.2 (0.2); *P* = 0.2799	49	0.4 (0.2); *P* = 0.0246
Overall, how satisfied are you with the inhaler?	53	–0.1 (0.2); *P* = 0.7749	47	–0.6 (0.3): *P* = 0.0160	48	0.3 (0.2); *P* = 0.0994
Convenience						
Satisfied with the inhaler's instructions?	52	–0.0 (0.1); *P* = 0.8496	47	–0.0 (0.1); *P* = 0.7994	49	0.0 (0.0); *P* = 0.3223
Satisfied with the inhaler size?	51	–0.3 (0.2); *P* = 0.1330	47	–0.2 (0.2); *P* = 0.3148	49	0.1 (0.1); *P* = 0.4167
Satisfied with the inhaler durability?	52	0.0 (0.1); *P* = 0.7490	46	0.1 (0.0); *P* = 0.0236	49	0.2 (0.1); *P* = 0.0484
Satisfied with the ease of cleaning the inhaler?	52	0.0 (0.1); *P* = 0.6419	47	0.1 (0.1); *P* = 0.3021	49	0.1 (0.1); *P* = 0.4852
Satisfied the inhaler is environmentally friendly?	52	0.2 (0.1); *P* = 0.0959	47	0.1 (0.1); *P* = 0.2093	49	0.4 (0.2); *P* = 0.0428
Satisfied with the ease of holding the inhaler during use?	53	0.1 (0.1); *P* = 0.7000	47	–0.1 (0.1); *P* = 0.3017	49	0.0 (0.2); *P* = 0.8944
Satisfied with the overall convenience of carrying the inhaler with you?	53	–0.4 (0.1); *P* = 0.0138	47	–0.2 (0.1); *P* = 0.1016	49	–0.2 (0.1); *P* = 0.0768

Diff = difference; Iprat 36 = ipratropium 36 mcg four times daily; MDI = metered dose inhaler; PL = placebo; Resp = Respimat; SE = standard error; Tio R 5 = Spiriva Respimat 5 mcg daily dose.

Notes: Scale: 1 = Very dissatisfied; 2 = Dissatisfied; 3 = Somewhat dissatisfied; 4 = Neither satisfied or dissatisfied; 5 = Somewhat satisfied; 6 = Satisfied; 7 = Very satisfied. Questionnaire was only administered at US sites; statistics are only for respondents rating both devices.

Source: Clinical Study Report 205.252.[12]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity and the MCID of the following outcome measures:

- Forced expiration volume in one second (FEV_1)
- St. George's Respiratory Questionnaire (SGRQ)
- Transition Dyspnea Index (TDI).

Findings

FEV_1, SGRQ, and TDI are briefly summarized in Table 61.

TABLE 61: VALIDITY AND MCID OF OUTCOME MEASURES

Instrument	Type	Validation Information	MCID	References
FEV_1	FEV_1 is the volume of air that, after a full inspiration, can be forcibly expired in one second.	Yes	0.10 L to 0.14 L	Cazzola et al. 2008[41]
SGRQ	The SGRQ is a disease-specific measure of HRQoL that consists of 50 items, and was specifically developed for patients with chronic airflow limitation. The SGRQ-COPD (SGRQ-C) is a well-established instrument for the assessment of health status in patients with COPD. The questionnaire is divided into three dimensions: symptoms, activity, and impacts of the disease. The total score ranges from 0 to 100, where 0 indicates no impairment and 100 indicate worst.	Yes	4.0	Menn et al. (2010),[51] Leidy et al. (2010),[52] Meguro et al. (2007),[53] Maly et al. 2006,[54]
TDI	The BDI is used to measured dyspnea at baseline and the TDI is used during the treatment period to assess changes from baseline. The BDI and TDI each have three domains: functional impairment, magnitude of task, and magnitude of effort. The BDI domains are rated from 0 (severe) to 4 (unimpaired), and the rates are summed for the baseline focal score ranging from 0 to 12; the lower the score, the greater the severity of dyspnea. The TDI domains are rated from –3 (major deterioration) to 3 (major improvement), and the rates are summed for the transition focal score ranging from –9 to 9; negative scores indicate deterioration. Scores for the BDI and TDI were obtained through interviews.	Yes	1 unit	Witek et al. (2003)[42]

BDI = Baseline Dyspnea Index; FEV_1 = forced expiration volume in 1 second; MCID = minimal clinically important difference; SGRQ = St. George's Respiratory Questionnaire; SGRQ-C = St. George Respiratory Questionnaire in COPD; TDI = Transition Dyspnea Index.

Forced Expiration Volume in One Second

FEV_1 is the volume of air that, after a full inspiration, can be forcibly expired in one second. It is commonly used both in clinical practice and in clinical trials, and is generally thought to correlate with COPD outcomes.[55,56] In clinical practice, FEV_1 is used to grade the risk of death in COPD patients.[57] The generally accepted MCID in FEV_1 is between 0.10 L and 0.14 L.[41] There is evidence that, for patients who

are undergoing COPD exacerbation, a 2-day increase of 0.10 L reduces the relative risk of treatment failure by 20%.[55] However, changes of the same magnitude are not always associated with clinically important differences in all studies.

While both pre- and post-bronchodilator FEV_1 values have been reported to be indicators of health status, risk of death, and measure of severity in COPD, the Global Initiative for Chronic Lung Disease (GOLD) criteria indicate that post-bronchodilator values should be used.[58] This is supported by evidence from a prospective study of 300 patients with COPD who were followed for at least one and a half years and who were evaluated every three months until the end of the study.[55] Predictors of mortality were analyzed. While FEV_1, body mass index (BMI), dyspnea score, and several other factors were shown to be predictors of mortality, multivariate analyses showed that post-bronchodilator per cent predicted FEV_1 was a significant independent predictor of both all-cause mortality and respiratory-cause mortality, whereas the pre-bronchodilator per cent predicted FEV_1 was not (all-cause mortality $P = 0.008$ versus 0.126; respiratory-cause mortality $P = 0.0016$ versus 0.302). Furthermore, with respect to GOLD classifications of disease severity, the discriminative ability of the GOLD severity classification was higher using post-bronchodilator per cent predicted FEV_1 than with pre-bronchodilator per cent predicted FEV_1 ($P = 0.009$ versus 0.131).

Normalized area under the curve (AUC) FEV_1 is an average of the measurement of bronchodilation over at least 80% of the duration of action after a single inhalation.[59] No information regarding the validity of this outcome or the minimal clinically important difference (MCID) was identified.

St. George's Respiratory Questionnaire

The SGRQ is a disease-specific measure of health-related quality of life (HRQoL) that consists of 50 items; it was specifically designed for patients with chronic airflow limitation.[51] It was developed in 1992 to measure impaired health and perceived well-being in patients with airway disease, and to meet the need for a sensitive measure of HRQoL.[60] The instrument has been used worldwide in studies and in clinical settings.[60] The SGRQ questionnaire includes questions regarding sleep disturbances, public embarrassment, and panic (which can be signs of depression or anxiety), as well as feeling like a nuisance to friends and family, employment, and recreation activities (which are indicative of social impact).[61]

The 50 items of the questionnaire are divided into three dimensions: symptoms (eight items measuring the distress due to respiratory symptoms), activity (16 items measuring the effect of disturbances on mobility and physical activity), and impacts (26 items measuring the psychosocial impact of the disease).[54] Items are weighted using empirically derived weights in order to determine the total SGRQ, which ranges from 0 to 100, where 0 indicates no impairment and 100 indicates worst possible health.[53,54] The generally accepted MCID for a change in total SGRQ from baseline is 4.0 units of change; a decrease in scores indicates an increase in HRQoL.[52] These have been examined as within-group measures, not between-group measures. As all estimates of clinical significance are subject to measurement error, sample error, and require value judgments, MCID should be interpreted with caution.[52] Also, it is unclear which between-group MCID would be appropriate. Component scores for the symptoms, activity, and impact domains can be calculated (also ranging from 0 to 100), in addition to the total score. In the symptoms domain, patients are asked to rate the appearance, frequency, and severity of respiratory symptoms (such as wheezing, breathlessness, cough) on a five-point scale in which the low scores indicate no symptoms and high scores indicate more severe symptoms.[54] A number of items in the symptoms component relate to the frequency of symptoms over the previous year.[62] Responses on the other two domains are mostly yes-no in nature. The activity domain deals with mobility and physical activity problems that either cause or are limited by breathlessness.[54] Impacts

covers aspects involved in social functioning and psychosocial disturbances resulting from obstructive airways disease (employment, panic, medication, and side effects).[54] Social functioning and psychosocial disturbances have been identified by patients as particularly troubling aspects of COPD. The SGRQ-COPD (SGRQ-C) is a well-established instrument for the assessment of health status in patients with COPD.[53] A difference of ≥ 4 points in the SGRQ-C total score versus placebo at study end, or a ≥ 4 points from baseline is considered to be the MCID for this measure.[40]

Baseline and Transition Dyspnea Indices

The Baseline Dyspnea Index (BDI) is used to measured dyspnea at baseline and the TDI is used during the treatment period to assess changes from baseline. The BDI and TDI each have three domains: functional impairment, magnitude of task, and magnitude of effort. The BDI domains are rated from 0 (severe) to 4 (unimpaired), and the rates are summed for the baseline focal score ranging from 0 to 12; the lower the score, the greater the severity of dyspnea. The TDI domains are rated from –3 (major deterioration) to 3 (major improvement), and the rates are summed for the transition focal score ranging from –9 to 9; negative scores indicate deterioration. Scores for the BDI and TDI were obtained through interviews.

Witek and Mahler (2003)[42] conducted a retrospective analysis of a cohort of COPD patients (N = 997) to assess the validity and MCID for the TDI. The study reported significant correlations between the BDI/TDI and scores of the Physician's Global Evaluation (PGE) and the SGRQ. The authors concluded that the TDI is a valid instrument and that a one-unit change in the TDI focal score represents the MCID.

Summary

FEV_1, SGRQ, and TDI have all been shown to be valid outcome measure for patients with COPD.
The suggested MCIDs for FEV_1, SGRQ, and TDI were 0.10 L to 0.14 L, four units' change from baseline, and one unit change from baseline, respectively.

APPENDIX 6: SUMMARY AND APPRAISAL OF MIXED TREATMENT COMPARISON

Two mixed treatment comparisons (MTCs) — by Oba et al.[63] and Dong et al.[11] — were identified that evaluated the relative risk of mortality[11] or risk of chronic obstructive pulmonary disease (COPD) exacerbations[63] with Spiriva Respimat compared with other long-acting muscarinic antagonists (LAMAs), long-acting beta-2 agonists (LABAs), inhaled corticosteroids (ICS), or placebo in the treatment of COPD. The following is a summary and critical appraisal of the methods and main findings of the two MTCs.

Summary of Mixed Treatment Comparison

Methods

Both MTCs were based on a systematic review. The literature search included MEDLINE database Scopus, CINAHL, and the Internet including the online trial registries of manufacturers of the aforementioned LAMA products,[63] or MEDLINE, CINAHL, and Cochrane library.[11] The main inclusion criteria for Dong et al.'s MTC[63] were RCTs of tiotropium Soft Mist Inhaler (also known as Spiriva Respimat [Tio R]), tiotropium HandiHaler (Tio H), LABAs, ICS, and ICS/LABA combination with at least a six-month treatment duration.[11] Oba et al.'s MTC[63] selected randomized controlled trials (RCTs) of at least 12 weeks' duration, comparing a LAMA with placebo or another LAMA. Study selection, data extraction, and quality assessment were performed by two reviewers through two levels of study screening in both studies.[11,63]

Mixed Treatment Comparison

In Oba et al.'s MTC,[11] the analyses were conducted with a Bayesian Markov chain Monte Carlo method and fitted with the Bayesian software in WinBUGS version 1.4.3 (Medical Research Council [MRC] Biostatistics Unit, Cambridge, UK). Each pair of treatments was compared by estimating a hazard ratio (HR) of the outcome. The reported outcomes were moderate-to-severe and severe exacerbations rate, expressed as the number of events per person-year.

In Dong et al.'s study,[63] Bayesian Markov chain Monte Carlo methods with fixed- and random-effects models were used for the MTC meta-analysis. Results were presented as the odds ratio (OR) and 95% credible intervals (CrI). The primary outcome was overall death and the secondary outcome was cardiovascular (CV) death. For each treatment, the probability of overall and CV death and the probability of being ranked as the riskiest intervention were also estimated. Subgroup analyses were performed based on treatment duration and severity of COPD. Meta-regression was conducted to adjust for demographic characteristics. Sensitivity analyses were performed by excluding trials with the ICS withdrawal design and by restricting the analyses to trials with objective adjudication of cause of death. STATA version 9.0 (StataCorp) and WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK) were used for direct comparisons and MTC meta-analyses, respectively.

Results

Study and Patient Characteristics

In Oba et al.'s study, 27 studies (N = 48,140) comparing four different LAMA formulations (glycopyrronium, aclidinium, Tio R, and Tio H) for moderate-to-severe exacerbations and 23 studies (N = 44,250) for severe exacerbations were included. The mean ages (range: 63.5 years to 65 years), proportion of male patients (range: 65% to 73.8%), the mean baseline FEV_1 (range: 1.02 litres to 1.5 litres), and FEV_1 per cent predicted (range: 38.7% to 53.6%) were similar across the studies. The definitions of COPD exacerbations were similar across the studies. Moderate COPD exacerbation was defined as

exacerbation requiring treatment with systemic corticosteroids and/or antibiotics, and severe COPD exacerbations were defined as exacerbations requiring an emergency room visit, hospitalization, or a COPD-related SAE. The treatments formed a closed network with the placebo as the central link. The authors reported that, in general, the risk of methodological bias in the included studies appeared moderate to low. Allocation concealment was appropriate in 19 studies and was unclear in eight studies. A total of 23 out of 27 studies presented intention-to-treat analyses and 24 studies were double-blinded (DB).

In Dong et al.'s MTC, a total of 42 studies (N = 52,516) reporting on overall deaths and 31 studies reporting on CV death were included in the MTC, in which, the treatments formed a network with placebo as the central link. Similar characteristics were reported across trials with different treatments (mean age 64 years, 73% men, 37% current smokers, one year study duration, and 44% of predicted value in FEV_1). Cochrane's risk-of-bias tool was used to assess the risk of bias of individual studies. All 42 trials were randomized, DB, with 24 trials reporting adequate randomization procedures. Forty-one trials stated the withdrawal rate, which varied across trials and treatment groups (with the lowest value of 17% in the Tio R groups and the highest values of 33% in the ICS and placebo groups). Twenty-eight trials described the fraction of patients lost to follow-up. Only six trials described objective adjudication of cause of death.

Outcomes

Moderate-to-Severe Chronic Obstructive Pulmonary Disease Exacerbations

Reported in Oba et al.'s MTC, all studies were included in the evaluation for moderate-to-severe exacerbations. A random-effects model was used because of lower deviance information criterion (DIC) scores as compared with a fixed- effects model. Results of the MTC are presented in Table 62. Overall, it was reported that all LAMAs statistically significantly reduced moderate-to-severe exacerbations compared with placebo. When comparing LAMAs with each other, no statistically significant differences in rates of moderate-to-severe exacerbations were reported (Table 62). Tio R was associated with the highest probability of being the best therapy (61.1%) and the surface under the cumulative ranking (SUCRA) value (84.1%) among all treatment strategies evaluated. However, it was emphasized by the authors that the 95% CrI of the posterior distribution for the ranking suggested that any of the LAMA formulations could be the best therapy among all comparators (Table 63).

In terms of severe COPD exacerbations reported in Oba et al.'s MTC, a random-effects model was also used because of lower DIC scores as compared with a fixed-effects model. TIO H 18 was the only LAMA reported to reduced severe exacerbations rate versus placebo (HR = 0.73; 95% CrI, 0.60 to 0.86) (Table 62). There were no statistically significant differences between the LAMAs with respect to rates of severe exacerbations when compared together (Table 62). Aclidinium bromide was associated with the highest probability of being the best therapy (68.4%) and highest SUCRA value (81.3%) among all treatment strategies evaluated. However, it was emphasized by the authors that the 95% CrI of the posterior distribution for the ranking suggested that any of the LAMA formulations could be the best therapy among all comparators.

TABLE 62: TREATMENT COMPARISONS WITHIN THE OBA ET AL. MTC — EFFECTS OF LAMAS ON MODERATE-TO-SEVERE AND SEVERE COPD EXACERBATIONS

	Exacerbations: Hazard Ratio (95% CrI)	
Treatment	**Moderate-to-Severe**	**Severe**
Compared with placebo		
TIO H	0.75 (0.68 to 0.84)	0.73 (0.60 to 0.86)
TIO R	0.67 (0.54 to 0.84)	0.77 (0.58 to 1.00)
Aclidinium	0.79 (0.63 to 0.98)	0.58 (0.30 to 1.16)
Glycopyrronium	0.72 (0.59 to 0.88)	0.81 (0.55 to 1.14)
Compared with TIO H		
TIO R	0.90 (0.71 to 1.13)	1.06 (0.81 to 1.41)
Aclidinium	1.05 (0.81 to 1.34)	0.80 (0.40 to 1.64)
Glycopyrronium	0.96 (0.80 to 1.16)	1.11 (0.78 to 1.54)
Compared with TIO R		
Aclidinium	1.17 (0.85 to 1.6)	0.75 (0.37 to 1.58)
Glycopyrronium	1.07 (0.80 to 1.43)	1.05 (0.67 to 1.58)
Compared with aclidinium		
Glycopyrronium	0.92 (0.68 to 1.24)	1.39 (0.63 to 2.95)
Only Including Studies ≥ 6 Months of Treatment		
Compared with placebo		
TIO H	0.76 (0.68 to 0.85)	0.73 (0.61 to 0.86)
TIO R	0.68 (0.54 to 0.85)	0.77 (0.59 to 0.98)
Aclidinium	0.81 (0.64 to 1.03)	0.29 (0.11 to 0.73)
Glycopyrronium	0.73 (0.60 to 0.89)	0.81 (0.55 to 1.14)
Compared with TIO H		
TIO R	0.89 (0.7 to 1.13)	1.05 (0.81 to 1.39)
Aclidinium	1.07 (0.82 to 1.38)	0.40 (0.15 to 1.02)
Glycopyrronium	0.96 (0.79 to 1.16)	1.11 (0.78 to 1.54)
Compared with TIO R		
Aclidinium	1.20 (0.86 to 1.67)	0.38 (0.14 to 0.99)
Glycopyrronium	1.08 (0.8 to 1.44)	1.06 (0.67 to 1.57)
Compared with aclidinium		
Glycopyrronium	0.90 (0.66 to 1.22)	2.76 (1.02 to 7.54)

CrI = credible interval; TIO H = tiotropium dry powder delivered through HandiHaler; TIO R = tiotropium Respimat.
Note: the exacerbation rate was expressed as the number of events per person-year.
Source: Oba et al.,[63] Table 2, p. 10.

TABLE 63: PROBABILITY OF BEST THERAPY, SUCRA VALUES, AND RANKING OF THERAPY IN PREVENTING CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATIONS (OBA ET AL. MTC)

Treatment	Probability of Best Therapy (%)	SUCRA Values (%)	Ranking (95% CrI)
Moderate-to-Severe Exacerbations (All Studies)			
Placebo	0	0.5	5 (5 to 5)
TIO H	4.6	53.6	3 (1 to 4)
TIO R	61.1	84.1	1 (1 to 4)
Aclidinium	9.6	44.6	4 (1 to 4)
Glycopyrronium	24.8	67.2	2 (1 to 4)
Severe Exacerbations (All Studies)			
Placebo	0	5.0	5 (4 to 5)
TIO H	13.9	66.6	2 (1 to 4)
TIO R	8.8	53.2	3 (1 to 4)
Aclidinium	68.4	81.3	1 (1 to 5)
Glycopyrronium	8.8	43.9	3 (1 to 5)
Severe Exacerbations (Studies of at Least 6 Months' Duration)			
Placebo	0	4.4	5 (4 to 5)
TIO H	1.8	62.0	2 (2 to 4)
TIO R	1.2	49.2	3 (2 to 4)
Aclidinium	95.9	97.8	1 (1 to 3)
Glycopyrronium	1.1	36.6	4 (2 to 5)

CrI = credible interval; SUCRA = surface under the cumulative ranking; TIO H = tiotropium dry powder delivered through HandiHaler; TIO R = tiotropium solution delivered through Respimat Soft Mist Inhaler.
Source: Oba et al.,[63] Table 3, p. 11.

All-cause Mortality and Cardiovascular Mortality

The results on mortality of the Dong et al. MTC are listed in Table 64. Patients using Tio R were reported to have had an increased risk of all-cause mortality compared with those receiving placebo (OR = 1.51; 95% CrI, 1.06 to 2.19) or those using Tio H (OR = 1.65; 95% CrI, 1.13 to 2.43), LABA (OR = 1.63; 95% CrI, 1.10 to 2.44), or ICS/LABA (OR = 1.90; 95% CrI, 1.28 to 2.86). In contrast, ICS/LABA demonstrated a beneficial profile versus placebo (OR = 0.80; 95% CrI, 0.67 to 0.94) or versus ICS (OR = 0.77; 95% CrI, 0.64 to 0.93). For cardiovascular mortality, patients on Tio R experienced a higher risk compared with placebo (OR = 2.07; 95% CrI, 1.09 to 4.16), Tio H (OR = 2.38; 95% CrI, 1.20 to 4.99), LABA (OR = 3.04; 95% CrI, 1.48 to 6.55), ICS/LABA (OR = 2.79; 95% CrI, 1.37 to 6.02), or ICS (OR = 2.39; 95% CrI, 1.18 to 5.12). In contrast, LABA had a decreased risk versus placebo (OR = 0.68; 95% CrI, 0.50 to 0.93).

Among all the treatments, Tio R showed the highest probability of overall and CV death (8% and 3.5%, respectively), with an approximate probability of 95% of being ranked as the riskiest treatment. In contrast, ICS/LABA had the lowest probability of overall death (4.5%), with a probability of 0% of being ranked as the riskiest treatment (Table 65).

Subgroup analyses restricted to trials with longer treatment duration and trials including patients with severe COPD showed similar results to the main analysis (Table 66). Three Tio R trials included a group treated with 5 mcg once daily, and two included a group treated with 10 mcg once daily. Use of 10 mcg once daily Tio R tended to be associated with a higher risk of overall death against all comparators; it is noteworthy that this is not a Health Canada–approved dose for Tio R. The MTC meta-regression adjusting for demographic characteristics did not substantially affect the magnitude or direction of the finding of increased mortality risk with Tio R versus other treatments. The sensitivity analyses, which

excluded trials with an ICS withdrawal design and restricted trials with objective adjudication of cause of death, yielded similar results to the main analysis.

TABLE 64: RISK OF ALL-CAUSE DEATH AND CARDIOVASCULAR DEATH FOR EACH PAIRWISE COMPARISON FROM THE DONG ET AL. MTC

	All-Cause Deaths (N = 42)		Cardiovascular Deaths (N = 31)	
Comparison	Direct Comparison OR (95% CI)	MTC RE OR (95% CrI)	Direct Comparison OR (95% CI)	MTC RE OR (95% CrI)
Compared With TIO R				
TIO H	–	1.66 (1.04 to 2.75)	–	2.18 (0.73 to 6.48)
LABA	–	1.61 (1.00 to 2.66)	–	2.80 (0.91 to 8.52)
ICS/LABA	–	1.93 (1.20 to 3.24)	–	3.00 (1.08 to 9.95)
ICS	–	1.55 (0.96 to 2.65)	–	2.31 (0.76 to 7.15)
PL	1.49 (1.05 to 2.11)	1.54 (1.01 to 2.43)	1.96 (1.07 to 3.60)	2.18 (0.91 to 6.19)
Compared With TIO H				
LABA	0.76 (0.55 to 1.06)	0.97 (0.74 to 1.26)	1.24 (0.49 to 3.12)	1.29 (0.67 to 2.41)
ICS/LABA	1.81 (1.07 to 3.05)	1.16 (0.88 to 1.55)	2.05 (0.97 to 4.34)	1.37 (0.77 to 2.92)
ICS	–	0.93 (0.71 to 1.31)	– 1.00	1.06 (0.52 to 2.20)
PL	0.93 (0.81 to 1.07)	0.93 (0.75 to 1.17)	0.81 (0.61 to 1.06)	1.00 (0.64 to 1.89)
Compared With LABA				
ICS/LABA	1.10 (0.91 to 1.32)	1.20 (0.95 to 1.54)	0.84 (0.59 to 1.20)	1.07 (0.64 to 2.16)
ICS	0.86 (0.71 to 1.04)	0.95 (0.75 to 1.32)	0.73 (0.50 to 1.07)	0.82 (0.44 to 1.64)
PL	0.90 (0.75 to 1.08)	0.95 (0.77 to 1.23)	0.67 (0.48 to 0.95)	0.78 (0.48 to 1.55)
Compared With ICS/LABA				
ICS	0.78 (0.64 to 0.94)	0.80 (0.62 to 1.03)	0.97 (0.68 to 1.39)	0.77 (0.36 to 1.38)
PL	0.81 (0.67 to 0.98)	0.80 (0.67 to 1.09)	0.81 (0.58 to 1.14)	0.73 (0.41 to 1.30)
Compared With ICS				
PL	1.01 (0.86 to 1.20)	1.00 (0.76 to 1.23)	0.88 (0.64 to 1.20)	0.94 (0.57 to 1.85)

CrI = credible interval; ICS = inhaled corticosteroid; LABA = long-acting beta-2 agonist; N = the number of trials reporting on each outcome; OR = odds ratio; PL = placebo; RE = random effects; TIO H = tiotropium dry powder delivered through HandiHaler; TIO R = tiotropium solution delivered through Respimat Soft Mist Inhaler.
Source: Dong et al.,[11] Table 2, p. 52.

TABLE 65: PROBABILITY OF ALL-CAUSE DEATH AND CARDIOVASCULAR DEATH AND PROBABILITY OF BEING RANKED AS THE RISKIEST INTERVENTION FOR EACH TREATMENT (DONG ET AL. MTC)

	All-Cause Deaths (N = 42)		Cardiovascular Deaths (N = 31)	
Treatment	Probability of Death % (95% CrI), RE	Probability of Being Ranked as the Riskiest Intervention, %, RE	Probability of Death % (95% CrI), RE	Probability of Being Ranked as the Riskiest Intervention, %, RE
TIO R	8.32 (2.51 to 24.46)	94.61	3.83 (0.90 to 15.63)	89.49
TIO H	5.18 (1.62 to 15.40)	0.79	1.79 (0.51 to 6.29)	4.74
LABA	5.34 (1.65 to 16.03)	1.30	1.40 (0.39 to 5.07)	1.04
ICS/LABA	4.50 (1.39 to 13.56)	0.06	1.29 (0.35 to 4.48)	0.31
ICS	5.52 (1.72 to 16.33)	2.57	1.70 (0.47 to 6.03)	3.60
PL	5.57 (1.77 to 16.26)	0.67	1.77 (0.55 to 5.49)	0.82

CrI = credible interval; ICS = inhaled corticosteroid; LABA = long-acting beta-2 agonist; N = the number of trials reporting on each outcome; PL = placebo; RE = random effects; TIO H = tiotropium dry powder delivered through HandiHaler; TIO R = tiotropium solution delivered through Respimat Soft Mist Inhaler.
Source: Dong et al.,[11] Table 3, p. 53.

TABLE 66: SUBGROUP ANALYSIS FOR RISK OF ALL-CAUSE DEATH AND CARDIOVASCULAR DEATH FOR EACH PAIRWISE COMPARISON FROM THE DONG ET AL. MTC

Comparison	All-Cause Deaths (N = 42)		Cardiovascular Deaths (N = 31)	
	Study Duration ≥ 1 Year (N = 27)	FEV_1 < 50% Predicted Value (N = 30)	Study Duration ≥ 1 Year (N = 18)	FEV_1 < 50% Predicted Value (N = 22)
	RE, OR (95% CrI)	RE, OR (95% CrI)	RE, OR (95% CrI)	RE, OR (95% CrI)
Compared With TIO R				
TIO H	1.65 (0.999 to 2.78)	1.67 (1.03 to 2.89)	2.04 (0.40 to 8.87)	2.25 (0.75 to 6.80)
LABA	1.66 (1.01 to 2.80)	1.65 (1.00 to 2.88)	2.82 (0.58 to 12.55)	3.07 (1.02 to 9.79)
ICS/LABA	2.02 (1.22 to 3.47)	1.98 (1.20 to 3.50)	3.11 (0.71 to 16.48)	3.19 (1.13 to 11.60)
ICS	1.58 (0.99 to 2.79)	1.57 (0.96 to 3.10)	2.33 (0.48 to 10.91)	2.63 (0.83 to 9.56)
PL	1.55 (1.02 to 2.47)	1.55 (1.01 to 2.52)	2.28 (0.71 to 9.28)	2.19 (0.90 to 6.29)
Compared With TIO H				
LABA	1.00 (0.75 to 1.35)	0.99 (0.74 to 1.33)	1.38 (0.53 to 3.80)	1.36 (0.72 to 2.69)
ICS/LABA	1.21 (0.90 to 1.70)	1.18 (0.87 to 1.64)	1.52 (0.64 to 4.98)	1.41 (0.79 to 3.25)
ICS	0.95 (0.71 to 1.42)	0.94 (0.68 to 1.50)	1.14 (0.40 to 3.72)	1.16 (0.54 to 2.91)
PL	0.93 (0.74 to 1.24)	0.93 (0.73 to 1.19)	1.10 (0.55 to 3.35)	0.97 (0.61 to 1.81)
Compared With LABA				
LABA-ICS	1.21 (0.94 to 1.61)	1.19 (0.92 to 1.58)	1.10 (0.53 to 3.08)	1.04 (0.61 to 2.12)
ICS	0.95 (0.74 to 1.35)	0.95 (0.72 to 1.44)	0.82 (0.31 to 2.33)	0.85 (0.44 to 1.90)
PL	0.93 (0.73 to 1.23)	0.94 (0.72 to 1.22)	0.80 (0.40 to 2.29)	0.71 (0.42 to 1.36)
Compared With ICS/LABA				
ICS	0.79 (0.60 to 1.10)	0.79 (0.60 to 1.20)	0.76 (0.24 to 1.87)	0.83 (0.37 to 1.64)
PL	0.77 (0.59 to 1.01)	0.79 (0.59 to 1.03)	0.73 (0.30 to 1.85)	0.69 (0.35 to 1.22)
Compared With ICS				
PL	0.98 (0.73 to 1.23)	0.99 (0.65 to 1.31)	0.97 (0.47 to 2.68)	0.83 (0.40 to 1.77)

CrI = credible interval; ICS = inhaled corticosteroid; LABA = long-acting beta-2 agonist; OR = odds ratio; PL = placebo; RE = random effect model; TIO H = tiotropium dry powder delivered through HandiHaler; TIO R = tiotropium solution delivered through Respimat Soft Mist Inhaler.
Source: Dong et al.,[11] Table 4, p. 54.

Critical Appraisal of Network Meta-analysis

The quality of the manufacturer-submitted network meta-analysis was assessed according to recommendations provided by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[64] The commentary for each of the relevant items identified by ISPOR for both MTCs is provided in Table 67.

Strengths

Both MTCs satisfied many of the ISPOR criteria. Both were based on a systematic review to identify all relevant studies. Validity of all individual studies was assessed. The analysis was conducted using an appropriate and well-reported methodology (i.e., Bayesian analysis models). The outcome measures assessed in the MTC were appropriate and consistent with the key efficacy assessments included in the Common Drug Review (CDR) review. Heterogeneity and inconsistency were assessed. Meta-regression sensitivity analyses adjusted for the important baseline characteristics, subgroup and/or sensitivity analysis were also performed. The DIC was used to compare model fit between the fixed- and random-effects models.

Limitations

Several potential limitations of Oba et al.'s study are discussed as follows. First, the number of exacerbations per person-year was used to assess the exacerbation rates. However, not all included studies reported number of exacerbations per person-year, such as in studies on aclidinium bromide, where severe exacerbations were reported as the number of patients instead of exacerbation event rates. Second, the clinical heterogeneity (such as trial duration, severity of COPD, all concomitant medications) of the trials included in the analysis might have affected the estimates of treatment effects. The meta-regression analysis to assess biases by systematic differences between studies was also compromised due to limited information reported in the original trials. Third, the HRs were similar for both consistency and inconsistency models, and there was considerable overlap in the 95% CrIs, suggesting that there was no evidence of inconsistency. However, this should be interpreted with caution as there may not have been sufficient power to detect inconsistency.

The limitations of Dong et al.'s study are discussed as follows. First, the validity of the MTC relies on the assumptions of the similarity of demographic characteristics across trials and the homogeneity of each relative treatment effect. However, the risk estimates were also consistent between pairwise meta-analysis comparisons and MTC in terms of direction and magnitude. Nevertheless, the influences from unmeasured covariates cannot be entirely ruled out. Given rare events and few trials for some comparisons, heterogeneity or publication bias may affect the results. Second, patients with significant diseases were excluded in all included trials, and half of the trials excluded patients with specific CV morbidities. This may limit the generalizability of the findings in real practice. Third, the withdrawal rates were variable across treatment groups, with the lowest value in the Tio R group. This may raise concerns about overestimating the relative risk of Tio R due to underestimating the mortality of placebo and other active treatments. However, the proportions of patients lost to follow-up were low across treatment groups. Moreover, vital status information was ascertained in all placebo-controlled trials of Tio R, even for patients who withdrew early. Therefore, the unfavourable bias for Tio R should be limited.

Summary

In Oba et al.'s MTC, it was reported that there were no statistically significant differences in preventing COPD exacerbations among LAMAs. In a subgroup analysis restricting studies to those that had a minimum of six months of treatment, glycopyrronium was associated with the greatest probability of being the least effective strategy, and aclidinium bromide was associated with the greatest probability of being the best therapy and highest SUCRA value in preventing severe exacerbations. LAMAs were less effective in preventing COPD exacerbations in studies which allowed concomitant use of LABA, suggesting that the concomitant use of LABAs may not enhance the efficacy of LAMAs in preventing COPD exacerbations, although patients who were on the combination of LABA and LAMA may represent patients with more severe COPD. In Dong et al.'s study, it was found that Tio R was associated with a 50% to 90% increased risk of all-cause death and a two-to-three times increased risk of CV death versus placebo and other inhaled medications. However, this may reflect a dose-response association with a greater risk associated with the unapproved Tio R 10. It may also reflect various potential limitations of the MTC, including assessment of rare events within relatively short-duration trials, and uncertain baseline risk given most (if not all) of the included studies excluded patients with relevant CV disease. Moreover, the findings of this analysis are at odds with the TIOSPIR study, a large, long-duration RCT designed to assess the mortality risk associated with Tio R versus Tio H. Hence, the findings and conclusions derived from the above two MTCs should be interpreted with caution.

TABLE 67: APPRAISAL OF NETWORK META-ANALYSIS USING ISPOR CRITERIA

ISPOR Checklist Item		Details and Comments for Both MTCs[11,63]
1	Are the rationale for the study and the objectives stated clearly?	• The rationale for conducting a network meta-analysis and the study objectives were clearly stated.
2	Does the methods section include the following? • Eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction • Validity of individual studies	• The eligibility criteria for individual RCTs were clearly stated. • No list of excluded studies and reasons for exclusion was provided in the systematic review. • Information sources and search strategy were well reported. • Methods for selection process, data extraction were clearly reported. • Validity of individual studies was assessed.
3	Are the outcome measures described?	• Outcomes assessed in the network meta-analysis were clearly stated. • Justification of the outcome measures was provided.
4	Is there a description of methods for analysis/synthesis of evidence? • Description of analyses methods/models • Handling of potential bias/inconsistency • Analysis framework	• A description of the statistical model was provided. • The report states that the DIC was used to compare the fixed-effects models with random-effects models. • Direct comparison data were not provided in Oba's MTC.[63] • Both direct and indirect comparison estimates of effect were presented.[11]
5	Are sensitivity analyses presented?	• Meta-regression sensitivity analyses were performed.
6	Do the results include a summary of the studies included in the network of evidence? • Individual study data? • Network of studies?	• Individual study or patient characteristics were provided. • A figure showing the network of studies was provided.
7	Does the study describe an assessment of model fit?	• Both fixed and random-effects models were considered with model selection based on the DIC model fit measure.
8	Are the results of the evidence synthesis presented clearly?	• The results of the analysis were clearly reported for each outcome measure including point estimates and 95% CrI as a measure of uncertainty.
9	Sensitivity/scenario analyses	• Results of the sensitivity analyses were presented.

CrI = credible interval; CSR = Clinical Study Report; DIC = deviance information criterion; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; MTC = mixed treatment comparison; RCT = randomized controlled trial.

APPENDIX 7: COMPARISON OF INHALER DEVICES FOR SPIRIVA RESPIMAT AND SPIRIVA HANDIHALER

Aim:
To describe the characteristics regarding ease of use and correct use of the Spiriva Respimat and Spiriva HandiHaler used in the patients with chronic obstructive pulmonary disease (COPD).

Findings:
The characteristics of the Spiriva Respimat and Spiriva HandiHaler inhaler are summarized below.

Characteristics of the Inhalers
Tiotropium dry powder for oral inhalation is delivered through the Spiriva HandiHaler.[7] The patient must open the dust cap, open the mouthpiece, remove a capsule containing tiotropium dry powder from a blister package, place the capsule in the inhaler, push and release a button to crush the capsule, fully exhale, then inhale the dry powder. In order to ensure the full dose is achieved, the patient must then fully exhale and inhale any remaining dry powder. There is no indicator that tells a patient that the dose has been properly loaded and is ready to inhale, but the patient should be able to hear the capsule vibrating as an indicator that the dose has been properly inhaled.

Tiotropium solution for oral inhalation is delivered through the Spiriva Respimat inhaler.[6] After inserting the cartridge, which contains the solution of tiotropium (60 puffs, equivalent to 30 doses), preparing Spiriva Respimat for the first time requires turning the clear base in the direction of the black arrows on the label until it clicks (half a turn), opening the green cap until it snaps fully open, then pointing the inhaler toward the ground, and pressing the dose-release button, then closing the green cap. These steps need to be repeated until an aerosol cloud is visible from the clear base. These steps must then be repeated three more times to ensure the inhaler is prepared for use. For daily use of the Spiriva Respimat inhaler, the patient must turn the clear base, open the cap, close their lips around the mouthpiece, press the dose-release button, and inhale. These steps should be performed two times (two puffs) to receive the proper dose of medicine.[6]

More details regarding the characteristics of each inhaler are included in Table 68.

TABLE 68: TIOTROPIUM DRY POWDER AND SOLUTION INHALER CHARACTERISTICS

Characteristic	Spiriva HandiHaler[7,65]	Spiriva Respimat[6]
Preloaded/ Multi-dose	No – Patient must remove the tablet from blister package and insert it into the inhaler.[a]	Yes – Preloaded cartridge contains 60 puffs of tiotropium (equal to 30 doses of 5 mcg tiotropium). Each puff delivers 2.5 mcg tiotropium.
Confirmation that dose is ready	No – Audible click indicating that the mouthpiece has been properly secured, but there is nothing to indicate that the dose is ready.	Yes – Observation of an aerosol cloud once the device is primed.
Confirmation of dose delivery	Yes – Patient can hear and feel the capsule vibrate in the device chamber; medication may taste sweet.	Yes – Patient may feel and/or taste the aerosol cloud of medication deposited in their throat and/or mouth.

Characteristic	Spiriva HandiHaler[7,65]	Spiriva Respimat[6]
Number of inhalations required	1, once daily	2, once daily
Requires step after inhalation	Yes – Patient must remove used capsule from the chamber after use.	Yes – Patient must close the green cap for storage until inhaler is used again.
Inhaler requires cleaning	Once per month	At least once per week

[a] Requires patient to peel the outer foil off the package, not push pill through the package.

Patient Preference for Use of Spiriva HandiHaler Versus Respimat Inhaler

In an open-label clinical observational study, Hanada et al.[43] conducted two surveys to investigate patient preference for using the HandiHaler and the Respimat devices in patients with COPD. The first questionnaire was administered to 57 patients with COPD, eight weeks after switching from the HandiHaler to the Respimat. A second questionnaire was administered to 39 of these patients who continued to use the Respimat for more than two years. In the first survey, it was found that 17.5% of patients preferred the HandiHaler and 45.6% preferred the Respimat. In the second survey, the number of patients who could handle the Respimat device well had substantially increased, and the number of patients who preferred the Respimat had increased to 79.5%. The authors concluded that the preference for the Respimat over HandiHaler increased with continued use.

In another study by Asakura et al.,[44] 34 patients with COPD who received 18 mcg Tio H once daily were enrolled in this study. Of them, 29 patients were followed until 12 weeks after switching. In general, both inhalers were considered by patients to be easy to use. Twenty-one patients replied that it was easier to handle the Respimat than the HandiHaler. It was also reported that dry mouth following administration was decreased after switching to Respimat. However, patients experienced cough just after inhalation with Respimat. The author concluded that there was no major problem in switching from the Spiriva HandiHaler to Respimat.

The limitations of these two studies on the patient preference and ease of use of inhalers include that they were based on the survey and observational studies[43,44] in which patient selection was not clearly reported. Furthermore, there was no active comparator, the study was not blinded, the outcome was based on patients' subjective reporting, and the sample size was relatively small. Therefore, the strength of the findings is considered weak and should be interpreted with caution. A randomized controlled, DB study is needed to further assess patients' preference on the use of the two Spiriva inhaler devices.

Summary

The Spiriva Respimat inhaler is a multi-dose, preloaded inhaler, whereas the HandiHaler requires the patient to load each dose capsule into the inhaler prior to use. The Spiriva Respimat inhaler delivers a mist of tiotropium, but the Spiriva HandiHaler delivers dry powder and requires the patient to generate sufficient inspiratory force to ensure the dose is properly administered. Two small observational studies suggested patients preferred to use Respimat over HandiHaler, or at least that there was no major problem in switching from HandiHaler to Respimat. However, due to the limitations of the study designs, as well as the small sample size, patients' preference with respect to using the two inhaler devices needs to be further evaluated.

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