Common Drug Review
Clinical Review Report

December 2015

Drug	tiotropium bromide monohydrate and olodaterol hydrochloride (Inspiolto 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 emphysema.
Listing request	For the long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema, if the following clinical criteria are met: • moderate to severe COPD as defined by spirometry; • inadequate response to a long-acting beta$_2$ agonist (LABA) or long-acting muscarinic antagonist (LAMA).
Dosage form(s)	Inhalation solution delivered via the Respimat inhaler (2.5 mcg tiotropium and 2.5 mcg olodaterol per actuation)
NOC date	May 28, 2015
Manufacturer	Boehringer Ingelheim Canada Ltd.

Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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ABBREVIATIONS

ACL	aclidinium
AE	adverse event
AUC	area under the curve
BDI	baseline dyspnea index
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CWRCE	constant work rate cycle ergometry
DIC	deviance information criterion
EET	exercise endurance time
ESWT	endurance shuttle walk test
FEV_1	forced expiratory volume in one second
FM	formoterol
FP	fluticasone propionate
FVC	forced vital capacity
GLY	glycopyrronium
GOLD	Global Initiative for Chronic Lung Disease
ICS	inhaled corticosteroids
IND	indacaterol
LABA	long-acting $beta_2$ agonist
LAMA	long-acting muscarinic antagonist
MCID	minimal clinically important difference
MD	mean difference
OLO	olodaterol hydrochloride
SAE	serious adverse event
SAL	salmeterol
SD	standard deviation
SE	standard error
SGRQ	St. George's Respiratory Questionnaire
TDI	transition dyspnea index
TIO	tiotropium bromide monohydrate
UMEC	umeclidinium
VI	vilanterol
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Chronic obstructive pulmonary disease (COPD) is a respiratory disorder found mostly in people with a history of cigarette smoking, characterized by progressive, partially reversible airway obstruction and often including other features such as lung hyperinflation, systemic manifestations, and increasing frequency and severity of exacerbations. There is significant overlap of COPD subtypes, with many individuals presenting with features of chronic bronchitis and emphysema. COPD is a leading cause of morbidity and mortality worldwide and is associated with high rates of admissions and readmissions to hospital. Patients' everyday life is affected, including their ability to breathe, talk, sleep, work, and socialize.

The goals of COPD management are to prevent disease progression, reduce frequency and severity of exacerbations, alleviate symptoms, improve exercise tolerance and daily activity, treat exacerbations and complications, improve health status, and reduce mortality. Management decisions are guided by disease severity (i.e., symptoms, disability, and spirometry) and the frequency of acute exacerbations. Bronchodilators form the mainstay of pharmacotherapy for COPD. Muscarinic antagonists and beta$_2$ agonists are often used in combination for maximal improvement in dyspnea and function. Tiotropium bromide monohydrate plus olodaterol hydrochloride (TIO/OLO, Inspiolto Respimat) is a long-acting muscarinic antagonist/long-acting beta$_2$ agonist (LAMA/LABA) fixed-dose combination available as a solution for oral inhalation. The recommended dose for TIO/OLO is 5/5 mcg once daily, given as two inhalations from the Respimat inhaler at the same time of day.

Indication under review
For the long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema.
Listing criteria requested by sponsor
For the long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema, if the following clinical criteria are met: • moderate to severe COPD as defined by spirometry; • inadequate response to a LABA or LAMA.

The objective of this review is to evaluate the beneficial and harmful effects of TIO/OLO for the maintenance treatment of patients with COPD, including chronic bronchitis and emphysema.

Results and Interpretation

Included Studies

Ten manufacturer-sponsored, double-blind, phase 3, randomized controlled trials conducted in patients with moderate to severe COPD were included in this review. Two replicate 52-week, parallel-group studies (TONADO 1 and TONADO 2) assessed the efficacy and safety of TIO/OLO 5/5 mcg versus its individual monocomponents, TIO 5 mcg and OLO 5 mcg, for the co-primary end points of trough forced expiratory volume in one second (FEV_1) and FEV_1 area under the curve over three hours ($AUC_{0–3h}$) at week 24. One Japanese 52-week, parallel-group study (Study 1237.22) assessed the safety of TIO/OLO 5/5 mcg versus OLO 5 mcg for Japanese regulatory purposes, but due to a number of limitations (i.e., primary outcome defined post hoc, lack of adequate power, lack of generalizability), the presentation of

data from this study is limited to Section 3.1 and Section 3.2.1 of this report. Two replicate phase 3b, 12-week, parallel-group studies, OTEMTO 1 and OTEMTO 2, assessed the efficacy and safety of TIO/OLO 5/5 mcg versus TIO 5 mcg and placebo for the primary end points of trough FEV_1, FEV_1 $AUC_{0–3h}$, and St. George's Respiratory Questionnaire (SGRQ) total score at the end of treatment. One six-week, crossover study (VIVACITO) assessed the 24-hour lung function profile of TIO/OLO 5/5 mcg versus its individual monocomponents and placebo for the primary end point of FEV_1 $AUC_{0–24h}$ at the end of treatment. Two replicate, six-week crossover studies (MORACTO 1 and MORACTO 2) were exercise endurance studies designed to assess TIO/OLO 5/5 mcg versus its individual monocomponents and placebo for the co-primary end points of inspiratory capacity at rest and exercise endurance time (EET) during cycle ergometry at the end of treatment. One 12-week, parallel-group study (TORRACTO) was an exercise endurance study designed to assess TIO/OLO 5/5 mcg versus placebo for the primary end point of EET during cycle ergometry, and a sub-study looking at EET during the endurance shuttle walk test was also conducted. One six-week, crossover double-dummy study (ENERGITO) assessed the efficacy and safety of TIO/OLO 5/5 mcg versus fluticasone propionate/salmeterol (FP/SAL) 250/50 mcg and FP/SAL 500/50 mcg for the primary end point of FEV_1 $AUC_{0–12h}$ at the end of treatment.

TIO/OLO 2.5/5 mcg and TIO 2.5 mcg were included as treatment groups in some studies, but these are not presented here, as neither dose has a Health Canada–approved indication for COPD.

All studies enrolled patients at least 40 years of age with moderate to severe COPD. TONADO 1, TONADO 2, and VIVACITO also included patients with very severe COPD. The exercise endurance studies limited enrolment to patients up to 75 years of age. Baseline characteristics were generally balanced across treatment groups within studies. For the crossover studies, a washout period of three weeks was implemented. All studies had a follow-up period of three weeks after the last dose of medication was administered. The primary end points for TONADO 1 and TONADO 2 were assessed at week 24 of 52, while the primary end points for the other studies were assessed at end of treatment.

One of the main limitations of the included studies was the short duration (most were 6 and 12 weeks), which may not be sufficient to assess key clinical outcomes such as mortality, quality of life, and COPD exacerbations, as well as infrequently occurring serious adverse events. As well, statistical testing of multiple secondary outcomes not included in the pre-specified hierarchical analysis plan might have suffered from an inflated type I error due to a lack of appropriate control. Although TONADO 1 and TONADO 2 were 52 weeks in duration, the primary outcomes were assessed at 24 weeks. There was a higher rate of discontinuations in the 12-week trials that included a placebo group (OTEMTO 1, OTEMTO 2, TORRACTO), which could have potentially disrupted the balance of patient characteristics from randomization. The three-week washout period employed for crossover studies was sufficient for TIO/OLO and the individual components, but may not have been sufficient to wash out FP/SAL in the ENERGITO study because the appropriate washout period for an inhaled corticosteroid component is uncertain. There were no studies with head-to-head comparisons of TIO/OLO 5/5 mcg and other LAMA/LABA combination therapies.

Efficacy

There were a greater number of deaths in the TONADO 1 and TONADO 2 studies than the other studies, likely due to the longer 52-week study duration within which to accrue such events. In TONADO 1 and TONADO 2, the number of deaths ranged from four to 10 across treatment groups. In OTEMTO 1, OTEMTO 2, MORACTO 2, and ENERGITO, one to two deaths occurred across treatment groups. No deaths occurred in the VIVACITO, MORACTO 1, and TORRACTO studies. The meaningfulness of mortality data from these studies was limited due to the short duration of most of the trials.

The frequency of COPD exacerbations is an important efficacy outcome in interventional studies for patients with COPD, particularly the events that lead to hospitalizations. COPD exacerbations were assessed as an efficacy outcome only in TONADO 1 and TONADO 2. All other studies reported the incidence of COPD exacerbations as part of the safety analyses. In TONADO 1 and TONADO 2, the annual rate of any exacerbation per patient-year was slightly lower in the TIO/OLO 5/5 mcg group (annual rate range [redacted] per patient-year) than in the monotherapy groups (annual rate range [redacted] per patient-year) at 52 weeks, but none of these differences was statistically significant (*P* value range 0.0678 to 0.9019). In the six- and 12-week studies, the proportion of patients with COPD exacerbations ranged from 3.9% to 12.1%, with higher proportions in the placebo groups compared with other treatment groups within placebo-controlled studies. The proportion of patients with COPD exacerbations requiring hospitalization (severe exacerbations) was low in all studies (range 0% to 7.3%) with no clear increase in any one group compared with another. Due to the short duration of the majority of included studies, there likely was not a long enough observational period to draw meaningful conclusions on COPD exacerbations.

In TONADO 1 and TONADO 2, the adjusted mean trough FEV_1 response at week 24 was statistically significantly greater in the TIO/OLO 5/5 mcg group compared with the TIO 5 mcg group (TONADO 1, mean difference [MD] 0.071 L; 95% confidence interval [CI], 0.047 to 0.094; $P < 0.0001$; TONADO 2, MD 0.050; 95% CI, 0.024 to 0.075; $P = 0.0001$) and the OLO 5 mcg group (TONADO 1, MD 0.082; 95% CI, 0.059 to 0.106; $P < 0.0001$; TONADO 2, MD 0.088; 95% CI, 0.063 to 0.113; $P < 0.0001$). Similar differences between the TIO/OLO 5/5 mcg group and the TIO 5 mcg and OLO 5 mcg groups were seen in mean trough FEV_1 response after 52 weeks of treatment. In OTEMTO 1 and OTEMTO 2, there was a statistically significantly greater mean trough FEV_1 response at week 12 in the TIO/OLO 5/5 mcg group compared with the placebo group (OTEMTO 1, MD 0.162 L; 95% CI, 0.124 to 0.200; $P < 0.0001$; OTEMTO 2, MD 0.166 L; 95% CI, 0.129 to 0.203; $P < 0.0001$). Trough FEV_1 response was not included in the statistical testing hierarchy in VIVACITO, the exercise endurance studies, and ENERGITO, but in general the TIO/OLO 5/5 mcg groups had a greater mean trough FEV_1 response than the TIO 5 mcg, OLO 5 mcg, and placebo groups at the end of treatment. In the ENERGITO study, the TIO/OLO 5/5 mcg group had a greater mean trough FEV_1 response at week 6 than the FP/SAL 500/50 mcg (MD 0.058 L; 95% CI, 0.034 to 0.082; $P < 0.0001$) and FP/SAL 250/50 mcg (MD 0.047 L; 95% CI, 0.022 to 0.071; $P = 0.0002$) groups. The results generally exceeded the clinically significant threshold of 0.10 L for the comparisons between TIO/OLO 5/5 mcg and placebo, but not for the comparisons between TIO/OLO 5/5 mcg and the monotherapy groups or TIO/OLO 5/5 mcg and the FP/SAL groups. However, there remains uncertainty with respect to the threshold for clinical significance for comparisons of FEV_1 outcomes between active comparator treatments. Slightly greater differences between TIO/OLO 5/5 mcg and the monotherapy groups and placebo (MD > 0.100 L for all comparisons) were seen in the change from baseline in FEV_1 AUC outcomes when measured from 0 to 3 hours (TONADO 1, TONADO 2, OTEMTO 1, and OTEMTO 2), 0 to 12 hours (VIVACITO), 12 to 24 hours (VIVACITO), and 0 to 24 hours (VIVACITO) after dosing. In ENERGITO, there was a statistically significantly greater change from baseline in FEV_1 $AUC_{0–12h}$, $AUC_{0–24h}$, and $AUC_{12–24h}$ for the TIO/OLO 5/5 mcg group compared with the FP/SAL groups, but this difference exceeded 0.100 L only for FEV_1 $AUC_{0–12h}$.

Dyspnea as measured by the transition dyspnea index (TDI) focal score was assessed in TONADO 1 and TONADO 2 at week 24, and OTEMTO 1 and OTEMTO 2 at week 12. Results were not consistent across the TONADO 1 and TONADO 2 trials, with a statistically significantly greater improvement in mean TDI focal score seen only in TONADO 1 for TIO/OLO 5/5 mcg compared with the TIO 5 mcg group ([redacted]) and OLO 5 mcg group (MD 0.721 units; 95% CI, 0.357 to 1.086; $P = 0.0001$), although this end point was not in the statistical testing hierarchy and is susceptible to

inflated type 1 error. In OTEMTO 1 and OTEMTO 2, there was a statistically significantly greater improvement in mean TDI focal score at week 12 for TIO/OLO 5/5 mcg compared with placebo. In TONADO 1, the proportions of TDI responders (TDI focal score ≥ 1; minimal clinically important difference [MCID]) were slightly greater [redacted]. In TONADO 2, there were no differences in responder rates between groups. In OTEMTO 1 and OTEMTO 2, there was a greater proportion of responders in the [redacted]. Dyspnea was measured using the modified Borg scale in the exercise endurance studies (MORACTO 1, MORACTO 2, TORRACTO) during cycle ergometry as the slope of intensity of breathing discomfort, and an improvement in dyspnea was seen for TIO/OLO 5/5 mcg compared with placebo, but this was statistically significant only in MORACTO 1 and MORACTO 2, and not in TORRACTO.

Health-related quality of life was assessed using SGRQ total score in TONADO 1, TONADO 2, OTEMTO 1, and OTEMTO 2. [redacted]. These differences did not meet the MCID of 4 points. Similar results were seen in TONADO 1 at week 52. In TONADO 2, there was no statistically significant difference in SGRQ total score at week 24 and week 52 between the TIO/OLO 5/5 mcg group and the other treatment groups. In OTEMTO 1 and OTEMTO 2, SGRQ total score at week 12 was lower in the TIO/OLO 5/5 mcg group compared with the placebo group (OTEMTO 1, MD –4.894; 95% CI, –6.904 to −2.884; $P < 0.0001$; OTEMTO 2, MD –4.564; 95% CI, −6.499 to –2.629; $P < 0.0001$). [redacted]. In OTEMTO 1 and OTEMTO 2, there was a greater proportion of responders in the TIO/OLO 5/5 mcg group (OTEMTO 1, 53.1%; OTEMTO 2, 51.8%) compared with the TIO 5 mcg group (OTEMTO 1, 41.7%; OTEMTO 2, 41.1%) and placebo group (OTEMTO 1, 31.2%; OTEMTO 2, 32.6%).

Exercise endurance was evaluated in MORACTO 1, MORACTO 2, and TORRACTO as the endurance time at end of treatment during cycle ergometry at 75% maximal work capacity two hours post-dose. In MORACTO 1 and MORACTO 2, there was a statistically significant increase in adjusted mean endurance time during constant work rate cycle ergometry (CWRCE) after six weeks for TIO/OLO 5/5 mcg compared with placebo (MORACTO 1, 20.9% increase; $P < 0.0001$; MORACTO 2, 13.4% increase; $P < 0.0001$). In MORACTO 2, there was also a statistically significant increase in adjusted mean endurance time during CWRCE after six weeks for TIO/OLO 5/5 mcg compared with OLO 5 mcg (11.1% increase; $P = 0.0009$). There was no increase in endurance time for TIO/OLO 5/5 mcg compared with TIO 5 mcg and OLO 5 mcg in MORACTO 1 and compared with TIO 5 mcg in MORACTO 2. In TORRACTO, there was a statistically significant increase in endurance time during CWRCE after 12 weeks compared with placebo (13.8% increase; $P = 0.0209$). The endurance shuttle walk test was performed in a subset of patients in TORRACTO, and the EET during endurance shuttle walk test to symptom limitation at a walking speed corresponding to 85% of predicted peak oxygen consumption after 12 weeks was a key secondary end point. After 12 weeks of treatment, the adjusted mean endurance time increased by 20.9% for TIO/OLO 5/5 mcg compared with placebo ($P = 0.0552$). The clinical significance of the exercise endurance test results is uncertain given the lack of a clearly defined MCID.

Lung volume was measured by inspiratory capacity at rest before cycle ergometry at end of treatment in the exercise endurance studies. In MORACTO 1 and MORACTO 2, there was a statistically significantly greater increase in inspiratory capacity at rest at week 6 for TIO/OLO 5/5 mcg compared with the monotherapy components and placebo. In TORRACTO, there was a greater increase in inspiratory capacity at rest at week 12 for TIO/OLO 5/5 mcg compared with placebo, but differences were considered descriptive because this testing fell below a non-significant parameter in the testing hierarchy.

There was no direct evidence available to assess the efficacy of TIO/OLO 5/5 mcg versus other LAMA/LABA combination therapies in the included studies. The manufacturer submitted a network meta-analysis (NMA) to compare the efficacy and safety of TIO/OLO 5/5 mcg with other LAMA/LABA fixed-dose combination therapies currently on the market, including aclidinium/formoterol 400/12 mcg, indacaterol/glycopyrronium 110/50 mcg, and umeclidinium/vilanterol 62.5/25 mcg. Comparative efficacy and safety were based on a measure of trough FEV_1, SGRQ total score, TDI focal score, COPD exacerbations, and discontinuations due to an adverse event. There were 76 studies that met eligibility criteria for inclusion in the NMA, and outcomes data were analyzed for durations of 24 or 26 (24/26) weeks and 48 or 52 (48/52) weeks where possible to allow for inclusion of more studies. There were no statistically or clinically significant differences in outcomes between TIO/OLO 5/5 mcg and the other LAMA/LABA fixed-dose combination therapies. However, there was clinical heterogeneity among the included studies due to the inclusion of studies with outcomes measured at different time points in the same networks and differing inclusion criteria between included studies. Moreover, there was limited information provided about how the various sources of heterogeneity were identified and accounted for in the NMA. Hence, the overall results of the NMA, in combination with the aforementioned limitations, indicate that there is no clear evidence of clinically relevant differences with respect to the outcomes associated with TIO/OLO and other LAMA/LABAs in the treatment of COPD.

Harms

Adverse events reported with TIO/OLO 5/5 mcg were generally similar with comparator treatments across studies. The 52-week parallel-group studies (TONADO 1 and TONADO 2) were the longest and had the highest proportion of patients experiencing an adverse event (AE), serious adverse event (SAE), withdrawal due to adverse event (WDAE), or notable harm. The proportion of patients experiencing an AE in the 52-week studies (TONADO 1 and TONADO 2) ranged from 72.3% to 79.4% across treatment groups. In the 12-week studies (OTEMTO 1, OTEMTO 2, and TORRACTO), the proportion of patients experiencing an AE ranged from 43.1% to 51.5%, with a slightly higher proportion of patients in the placebo groups compared with the other treatment groups. In the six-week studies (VIVACITO, MORACTO 1, MORACTO 2, and ENERGITO), the proportion of patients experiencing an AE ranged from 29.7% in the FP/SAL 250/500 mcg group of ENERGITO to 46.4% in the placebo group of VIVACITO. The most common AEs across all trials were COPD exacerbations and nasopharyngitis.

In the 52-week studies (TONADO 1 and TONADO 2), the proportion of patients experiencing SAEs ranged from 14.2% to 20.8% across treatment groups. In the other six- and 12-week studies, the proportion of patients experiencing an SAE ranged from 0.7% to 5.9%. Generally, the proportion of patients experiencing an SAE across treatment groups within studies was balanced. In the 52-week studies (TONADO 1 and TONADO 2), the proportion of patients who withdrew due to an AE ranged from 7.1% to 10.6% across treatment groups. In the other six- and 12-week studies, the proportion of patients who withdrew due to an AE ranged from 0.5% to 6.1%. Generally, a higher proportion of patients in the placebo groups withdrew due to an AE compared with the other treatment groups.

The proportion of patients experiencing a cardiovascular-related event was low across all studies. In the 52-week studies (TONADO 1 and TONADO 2), the most common cardiovascular-related event was hypertension, and the proportion of patients experiencing hypertension ranged from 2.2% to 5.1% across treatment groups. Anticholinergic effects were generally rare across treatment groups and studies, ranging from 0% to 2.2% of patients across all treatment groups and studies. Cases of pneumonia were similarly rare across study groups and trials, ranging from 0% to 4.2% of patients affected. There were no safety data beyond 52 weeks, which may limit the observation of cardiovascular AEs and pneumonia.

Potential Place in Therapy[1]

Bronchodilators remain the mainstay of therapy for symptomatic patients with COPD. There are currently five combinations of an inhaled beta$_2$ agonist and anticholinergic drug that have been approved for the treatment of COPD. Although no head-to-head comparative study has been performed at this time, the submitted NMA suggests that TIO/OLO is as effective as the other once-per-day or twice-per-day combinations of an inhaled beta$_2$ agonist and anticholinergic, albeit noting the several limitations of this analysis.

TIO/OLO, like other combinations of a LABA and LAMA, should be considered in patients with COPD who remain symptomatic while employing either a LAMA or a LABA.

Conclusions

Ten manufacturer-sponsored, double-blind, phase 3, randomized controlled trials comparing TIO/OLO 5/5 mcg with its individual monocomponents, placebo, or FP/SAL met inclusion criteria for this review. Overall, the evidence was limited for key outcomes such as mortality, health care resource utilization, and COPD exacerbations, largely because the studies were not designed to assess these. There were statistically significant improvements in lung function with TIO/OLO 5/5 mcg compared with the monocomponents, placebo, and FP/SAL, as measured by trough FEV$_1$ at week 24 in TONADO 1 and TONADO 2 and at the end of treatment for the other studies. Health-related quality of life as assessed by SGRQ total score was not consistent between TONADO 1 and TONADO 2, with only TONADO 1 reporting statistically significant improvements from baseline at week 24 with TIO/OLO 5/5 mcg compared with the monotherapy components. Results from the exercise endurance studies demonstrated an improvement in EET during cycle ergometry with TIO/OLO 5/5 mcg compared with placebo but not compared with the monotherapy groups. The most common AEs in the included trials were nasopharyngitis and COPD exacerbations. SAEs and WDAEs were generally low and balanced between treatment groups, with a slightly higher rate of withdrawals in the placebo groups. The frequencies of cardiovascular effects, anticholinergic effects, and cases of pneumonia with TIO/OLO 5/5 mcg were very low, in part a reflection of the short duration of most of the studies. No data beyond 52 weeks were available. A manufacturer-submitted NMA suggested no difference in efficacy between TIO/OLO 5/5 mcg and other LAMA/LABA combination therapies with respect to trough FEV$_1$, SGRQ total score, TDI focal score, COPD exacerbations, and discontinuations due to AEs at 24/26 weeks and 48/52 weeks time points. However, there was clinical heterogeneity among the included studies due to the inclusion of studies with outcomes measured at different time points in the same networks and differing inclusion criteria between included studies. Hence, there is no clear evidence of clinically relevant

[1] This information is based on information provided in draft form by the clinical expert consulted by CADTH Common Drug Review (CDR) reviewers for the purpose of this review.

differences with respect to the outcomes associated with TIO/OLO and other LAMA/LABAs in the treatment of COPD.

TABLE 1: SUMMARY OF RESULTS — 52-WEEK PARALLEL-GROUP STUDIES (TONADO 1, TONADO 2)

Outcome	TONADO 1 (1237.5)			TONADO 2 (1237.6)		
	TIO/OLO 5/5 mcg (N = 522)	TIO 5 mcg (N = 527)	OLO 5 mcg (N = 528)	TIO/OLO 5/5 mcg (N = 507)	TIO 5 mcg (N = 506)	OLO 5 mcg (N = 510)
Deaths, n (%)	9 (1.7)	9 (1.7)	4 (0.8)	9 (1.8)	8 (1.6)	10 (2.0)
COPD exacerbations, n (%)						
Any exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Annual rate/PY (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Requiring hospitalization	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Annual rate/PY (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FEV_1 $AUC_{0–3h}$ response (L), week 24, *co-primary end point*						
N[a]	522	526	525	502	500	507
Common baseline mean (SE)[a]		[redacted]			[redacted]	
Adjusted mean response (SE)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	0.117 (0.094 to 0.140)	0.123 (0.100 to 0.146)	-	0.103 (0.078 to 0.127)	0.132 (0.108 to 0.157)
P value	-	< 0.0001	< 0.0001	-	< 0.0001	< 0.0001
Trough FEV_1 response (L), week 24, *co-primary end point*						
N[a]	521	520	519	497	498	503
Common baseline mean (SE)[a]		[redacted]			[redacted]	
Adjusted mean response (SE)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	0.071 (0.047 to 0.094)	0.082 (0.059 to 0.106)	-	0.050 (0.024 to 0.075)	0.088 (0.063 to 0.113)
P value	-	< 0.0001	< 0.0001	-	0.0001	< 0.0001
TDI focal score, week 24						
N	509	498	503	484	480	481
Common baseline mean (SE)[a]		[redacted]			[redacted]	
Adjusted mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Outcome	TONADO 1 (1237.5)			TONADO 2 (1237.6)		
	TIO/OLO 5/5 mcg (N = 522)	TIO 5 mcg (N = 527)	OLO 5 mcg (N = 528)	TIO/OLO 5/5 mcg (N = 507)	TIO 5 mcg (N = 506)	OLO 5 mcg (N = 510)
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	[redacted]	[redacted]	-	[redacted]	[redacted]
P value	-	[redacted]	[redacted]	-	[redacted]	[redacted]
Responder, n (%)[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SGRQ total score, week 24						
N	502	486	483	478	468	471
Common baseline mean (SE)[a]	[redacted]			[redacted]		
Adjusted mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	[redacted]	[redacted]	-	[redacted]	[redacted]
P value	-	[redacted]	[redacted]	-	[redacted]	[redacted]
Responder, n (%)[e]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Harms						
AEs, n (%)	387 (74.1)	381 (72.3)	390 (73.9)	374 (73.8)	376 (74.3)	405 (79.4)
SAEs, n (%)	87 (16.7)	79 (15.0)	75 (14.2)	82 (16.2)	93 (18.4)	106 (20.8)
WDAEs, n (%)	37 (7.1)	42 (8.0)	49 (9.3)	39 (7.7)	51 (10.1)	54 (10.6)
Notable harms, n (%)						
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	19 (3.6)	19 (3.6)	22 (4.2)	15 (3.0)	7 (1.4)	14 (2.7)

AE = adverse event; AUC = area under the curve; CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; MD = mean difference; MMRM = mixed model for repeated measures; OLO = olodaterol; PY = patient-year; SAE = serious adverse event; SE = standard error; SGRQ = St. George's Respiratory Questionnaire; TDI = transition dyspnea index; TIO = tiotropium; vs. = versus; WDAE = withdrawal due to adverse event.

[a] Number of patients contributing to MMRM; baseline mean calculated from all patients contributing to MMRM.

[b] MMRM including treatment, planned test day, treatment-by-test-day interaction, baseline, and baseline-by-test-day interaction as fixed effects, and patient as random effect.

[c] No control for statistical testing, outside of the testing hierarchy.

[d] Defined as TDI focal score ≥ 1.

[e] Defined as an improvement of SGRQ total score ≥ 4.0 from baseline.

Source: Clinical Study Reports.[1,2]

TABLE 2: SUMMARY OF RESULTS — 12-WEEK PHASE 3B STUDIES (OTEMTO 1, OTEMTO 2)

Outcome	OTEMTO 1 (1237.25)			OTEMTO 2 (1237.26)		
	TIO/OLO 5/5 mcg (N = 203)	TIO 5 mcg (N = 203)	Placebo (N = 204)	TIO/OLO 5/5 mcg (N = 202)	TIO 5 mcg (N = 203)	Placebo (N = 202)
Deaths, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COPD exacerbations, n (%)						
Any exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Requiring hospitalization	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FEV_1 $AUC_{0–3h}$ response (L), week 12, *co-primary end point*						
N[a]	202	203	204	200	201	199
Common baseline mean (SE)[a]	1.296 (0.018)			1.323 (0.017)		
Adjusted mean response (SE)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	0.111 (0.075 to 0.148)	0.331 (0.293 to 0.369)	-	0.105 (0.069 to 0.141)	0.299 (0.261 to 0.336)
P value	-	< 0.0001[c]	< 0.0001	-	< 0.0001[c]	< 0.0001
Trough FEV_1 response (L), week 12, *co-primary end point*						
N[a]	200	200	198	199	197	193
Common baseline mean (SE)[a]	1.298 (0.018)			1.329 (0.017)		
Adjusted mean response (SE)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	0.028 (−0.009 to 0.066)	0.162 (0.124 to 0.200)	-	0.039 (0.002 to 0.076)	0.166 (0.129 to 0.203)
P value	-	0.1381[c]	< 0.0001	-	0.0395[c]	< 0.0001
TDI focal score, week 12, *secondary end point*						
N	196	193	187	197	192	183
Common baseline mean (SE)[a]	6.421 (0.073)			6.653 (0.075)		
Adjusted mean (SE)	1.939 (0.190)	1.332 (0.192)	−0.113 (0.196)	1.531 (0.187)	0.950 (0.191)	0.337 (0.195)
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	0.607 (0.078 to 1.137)	2.052 (1.516 to 2.588)	-	0.582 (0.058 to 1.106)	1.195 (0.665 to 1.725)
P value	-	0.0246[c]	< 0.0001[c]	-	0.0296[c]	< 0.0001[c]
Responder, n (%)[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Outcome	OTEMTO 1 (1237.25)			OTEMTO 2 (1237.26)		
	TIO/OLO 5/5 mcg (N = 203)	TIO 5 mcg (N = 203)	Placebo (N = 204)	TIO/OLO 5/5 mcg (N = 202)	TIO 5 mcg (N = 203)	Placebo (N = 202)
SGRQ total score, week 12, a*dditional end point*						
N	196	192	186	197	192	184
Common baseline mean (SE)[a]	42.433 (0.622)			42.700 (0.617)		
Adjusted mean (SE)	37.144 (0.710)	39.637 (0.717)	42.038 (0.738)	38.011 (0.683)	39.729 (0.694)	45.575 (0.711)
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	−2.493 (−4.473 to −0.513)	−4.894 (−6.904 to −2.884)	-	−1.717 (−3.628 to 0.193)	−4.564 (−6.499 to −2.629)
P value	-	0.0136[c]	< 0.0001	-	0.0780[c]	< 0.0001
Responder, n (%)[e]	104 (53.1)	80 (41.7)	58 (31.2)	102 (51.8)	79 (41.1)	60 (32.6)
Harms						
AEs, n (%)	91 (44.8)	90 (44.3)	105 (51.5)	87 (43.1)	93 (45.8)	93 (46.0)
SAEs, n (%)	10 (4.9)	6 (3.0)	11 (5.4)	6 (3.0)	12 (5.9)	4 (2.0)
WDAEs, n (%)	3 (1.5)	3 (1.5)	11[a] (5.4)	1 (0.5)	7 (3.4)	10 (5.0)
Notable harms, n (%)						
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; AUC = area under the curve; CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; MD = mean difference; MMRM = mixed model for repeated measures; OLO = olodaterol; PY = patient-year; SAE = serious adverse event; SE = standard error; SGRQ = St. George's Respiratory Questionnaire; TDI = transition dyspnea index; TIO = tiotropium; vs. = versus; WDAE = withdrawal due to adverse event.

[a] Number of patients contributing to MMRM; baseline mean calculated from all patients contributing to MMRM.

[b] MMRM including treatment, planned test day, treatment-by-test-day interaction, baseline, and baseline-by-test-day interaction as fixed effects, and patient as random effect.

[c] No control for statistical testing, outside the testing hierarchy.

[d] Defined as TDI focal score ≥ 1.

[e] Defined as an improvement of SGRQ total score ≥ 4.0 from baseline.

Source: Clinical Study Reports.[3,4]

TABLE 3: SUMMARY OF RESULTS — SIX-WEEK LUNG FUNCTION PROFILE CROSSOVER STUDY (VIVACITO)

Outcome	VIVACITO (1237.20)			
	TIO/OLO 5/5 mcg (n = 139)	TIO 5 mcg (n = 138)	OLO 5 mcg (n = 138)	Placebo (n = 138)
Deaths, n (%)	0	0	0	0
COPD exacerbations, n (%)				
Any exacerbation	[redacted]	[redacted]	[redacted]	[redacted]
Requiring hospitalization	[redacted]	[redacted]	[redacted]	[redacted]
FEV_1 $AUC_{0–24h}$ response (L), week 6, *primary end point*				
N[a]	138	135	136	132
Common baseline mean (SE)[a]	1.301 (0.030)			
Adjusted mean response (SE)[b]	0.244 (0.013)	0.133 (0.014)	0.129 (0.013)	−0.037 (0.014)
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	0.110 (0.082 to 0.139)	0.115 (0.087 to 0.143)	0.280 (0.252 to 0.309)
P value	-	< 0.0001	< 0.0001	< 0.0001
Trough FEV_1 response (L), week 6, *additional end point*				
N[a]	138	135	136	132
Common baseline mean (SE)[a]	1.301 (0.030)			
Adjusted mean response (SE)[b]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	0.079 (0.045 to 0.113)	0.092 (0.059 to 0.126)	0.207 (0.173 to 0.241)
P value	-	[redacted]	[redacted]	[redacted]
Harms				
AEs, n (%)	52 (37.4)	61 (44.2)	52 (37.7)	64 (46.4)
SAEs, n (%)	1 (0.7)	3 (2.2)	8 (5.8)	4 (2.9)
WDAEs, n (%)	1 (0.7)	2 (1.4)	3 (2.2)	5 (3.6)
Notable harms, n (%)				
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; AUC = area under the curve; CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; MD = mean difference; MMRM = mixed model for repeated measures; OLO = olodaterol; SAE = serious adverse event; SE = standard error; TIO = tiotropium; vs. = versus; WDAE = withdrawal due to adverse event.

[a] Number of patients with measurements available at week 6; baseline mean calculated from all patients with measurements available at week 6.

[b] MMRM with treatment and period as fixed effects, patient baseline and period baseline as covariates, and patient as random effect.

[c] No control for statistical testing, outside of the testing hierarchy.

Source: Clinical Study Report.[5]

TABLE 4: SUMMARY OF RESULTS — SIX-WEEK CROSSOVER EXERCISE TOLERANCE STUDIES (MORACTO 1, MORACTO 2)

Outcome	MORACTO 1 (1237.13)				MORACTO 2 (1237.14)			
	TIO/ OLO 5/5 mcg	TIO 5 mcg	OLO 5 mcg	Placebo	TIO/ OLO 5/5 mcg	TIO 5 mcg	OLO 5 mcg	Placebo
N	226	226	217	222	224	218	218	214
Deaths, n (%)	[redacted]							
COPD exacerbations, n (%)								
Any exacerbation	[redacted]							
Requiring hospitalization	[redacted]							
Trough FEV_1 response (L), week 6, *additional end point*								
N[a]	[redacted]							
Common baseline mean (SE)[a]	[redacted]							
Adjusted mean (SE)[b]	[redacted]							
Adjusted MD (95% CI), TIO/OLO vs. comparator	[redacted]							
P value	[redacted]							
IC at rest (L), week 6, *co-primary end point*								
N[a]	219	213	214	211	218	208	208	202
Common baseline mean (SE)[a]	2.533 (0.042)				2.589 (0.044)			
Adjusted mean (SE)[b]	2.685 (0.027)	2.571 (0.027)	2.566 (0.027)	2.440 (0.027)	2.767 (0.025)	2.679 (0.025)	2.687 (0.025)	2.502 (0.026)
Adjusted MD (95% CI), TIO/OLO vs. comparator	[redacted]							
P value	[redacted]							
EET during CWRCE at 75% Wcap (seconds), week 6, *co-primary end point*								
N[a]	212	209	208	209	216	209	207	205
Common baseline mean (SE)[a]	459.95 (13.941)				434.31 (14.163)			
Adjusted mean (SE)[b,d]	454.08 (14.474)	457.16 (14.652)	453.38 (14.552)	375.45 (12.037)	465.68 (13.359)	446.50 (12.958)	419.06 (12.207)	410.77 (12.009)
Adjusted mean ratio (95% CI),	[redacted]							

Outcome	MORACTO 1 (1237.13)				MORACTO 2 (1237.14)			
	TIO/ OLO 5/5 mcg	TIO 5 mcg	OLO 5 mcg	Placebo	TIO/ OLO 5/5 mcg	TIO 5 mcg	OLO 5 mcg	Placebo
TIO/OLO vs. comparator[d]								
P value	-	0.8415	0.9633	< 0.0001	-	0.1807	0.0009	< 0.0001
Slope of intensity of breathing discomfort during CWRCE (units/second)[e], week 6, *secondary end point*								
N[a]	[redacted]							
Common baseline mean slope (SE)[a]	[redacted]							
Adjusted mean (SE)[b]	[redacted]							
Adjusted MD (95% CI), TIO/OLO vs. comparator	[redacted]							
P value	[redacted]							
Harms								
AEs, n (%)	[redacted]							
SAEs, n (%)	[redacted]							
WDAEs, n (%)	[redacted]							
Notable harms, n (%)								
Cardiac disorders	[redacted]							
Hypertension	[redacted]							
Dizziness	[redacted]							
Dry mouth	[redacted]							
Pneumonia	[redacted]							

AE = adverse event; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CWRCE = constant work rate cycle ergometry; EET = exercise endurance time; FEV_1 = forced expiratory volume in 1 second; IC = inspiratory capacity; MD = mean difference; OLO = olodaterol; SAE = serious adverse event; SE = standard error; TIO = tiotropium; vs. = versus; Wcap = maximal work capacity; WDAE = withdrawal due to adverse event.

[a] Number of patients contributing to the MMRM model; baseline mean calculated from all patients contributing to MMRM.

[b] MMRM with treatment and period as fixed effects, study baseline as covariate, patient as random effect, and compound symmetry as a covariance structure for within-patient variation.

[c] No control for statistical testing, outside of the testing hierarchy.

[d] Mean and confidence intervals were transformed from $\log_{10}$ back to the original scale.

[e] Defined as (Borg scale of breathing discomfort at the end of exercise minus Borg scale of breathing discomfort at pre-exercise)/endurance time.

Source: Clinical Study Reports.[6,7]

TABLE 5: SUMMARY OF RESULTS — 12-WEEK PARALLEL-GROUP EXERCISE TOLERANCE STUDY (TORRACTO)

Outcome	TORRACTO (1237.15)	
	TIO/ OLO 5/5 mcg (n = 139)	Placebo (n = 132)
Deaths, n (%)	0	0
COPD exacerbations, n (%)		
Any exacerbation	[redacted]	[redacted]
Requiring hospitalization	[redacted]	[redacted]
Trough FEV_1 response (L), week 12, *additional end point*		
N[a]	[redacted]	[redacted]
Common baseline mean (SE)[a]	[redacted]	
Adjusted mean (SE)[b]	[redacted]	[redacted]
Adjusted MD (95% CI), TIO/OLO vs. comparator	[redacted]	[redacted]
P value	[redacted]	[redacted]
IC at rest before CWRCE (L), week 12, *secondary end point*		
N[a]	[redacted]	[redacted]
Common baseline mean (SE)[a]	[redacted]	
Adjusted mean (SE)[b]	[redacted]	[redacted]
Adjusted MD (95% CI), TIO/OLO vs. comparator	[redacted]	[redacted]
P value	[redacted]	[redacted]
EET during CWRCE at 75% Wcap (seconds), week 12, *primary end point*		
N[a]	135	121
Common baseline mean (SE)[a]	443.0 (12.38)	
Adjusted mean (SE)[b,d]	527.51 (20.154)	463.63 (18.813)
Adjusted mean ratio (95% CI), TIO/OLO vs. comparator[d]	-	1.138 (1.020 to 1.269)
P value	-	0.0209
EET during ESWT at 85% VO_2 peak (seconds)[f], week 12, *secondary end point*		
N[a]	59	50
Common baseline mean (SE)[a]	311.2 (13.68)	
Adjusted mean (SE)[b,d]	376.39 (25.033)	311.41 (22.519)
Adjusted mean ratio (95% CI), TIO/OLO vs. comparator[d]	-	1.209 (0.996 to 1.467)
P value	-	0.0552[g]
Slope of intensity of breathing discomfort during CWRCE (units/second)[e], week 12, *secondary end point*		
N[a]	[redacted]	[redacted]
Common baseline mean slope (SE)[a]	[redacted]	
Adjusted mean (SE)[b]	[redacted]	[redacted]
Adjusted MD (95% CI), TIO/OLO vs. comparator	[redacted]	[redacted]
P value	[redacted]	[redacted]
Harms		
AEs, n (%)	[redacted]	[redacted]

Outcome	TORRACTO (1237.15)	
	TIO/ OLO 5/5 mcg (n = 139)	Placebo (n = 132)
SAEs, n (%)	[redacted]	[redacted]
WDAEs, n (%)	[redacted]	[redacted]
Notable harms, n (%)		
Cardiac disorders	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]

AE = adverse event; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CWRCE = constant work rate cycle ergometry; EET = exercise endurance time; ESWT = endurance shuttle walk test; FEV_1 = forced expiratory volume in 1 second; IC = inspiratory capacity; MD = mean difference; OLO = olodaterol; SAE = serious adverse event; SE = standard error; TIO = tiotropium; VO_2 peak = maximal oxygen consumption; Wcap = maximal work capacity; vs. = versus; WDAE = withdrawal due to adverse event.
[a] Number of patients contributing to the MMRM model; baseline mean calculated from all patients contributing to MMRM.
[b] MMRM including treatment, planned test day, treatment-by-test-day interaction, baseline, and baseline-by-test-day interaction as fixed effects, patient as random effect, and compound symmetry as covariance structure for within-patient variation.
[c] No control for statistical testing, outside of the testing hierarchy.
[d] Mean and confidence intervals were transformed from log_{10} back to the original scale.
[e] Defined as (Borg scale of breathing discomfort at the end of exercise minus Borg scale of breathing discomfort at pre-exercise)/endurance time.
[f] Conducted at select centres.
[g] Descriptive as outcome fell below a statistically non-significant parameter in the testing hierarchy.
Source: Clinical Study Report.[8]

TABLE 6: SUMMARY OF RESULTS — SIX-WEEK TIOTROPIUM/OLODATEROL VERSUS FLUTICASONE PROPIONATE/SALMETEROL CROSSOVER STUDY (ENERGITO)

Outcome	ENERGITO (1237.11)		
	TIO/OLO 5/5 mcg (n = 221)	FP/SAL 500/50 mcg (n = 219)	FP/SAL 250/50 mcg (n = 212)
Deaths, n (%)	2 (0.9)	0	0
COPD exacerbations, n (%)			
Any exacerbation	[redacted]	[redacted]	[redacted]
Requiring hospitalization	[redacted]	[redacted]	[redacted]
FEV_1 $AUC_{0–12h}$ response (L), week 6, *primary end point*			
N[a]	[redacted]	[redacted]	[redacted]
Common baseline mean (SE)[a]	[redacted]		
Adjusted mean (SE)[b]	[redacted]	[redacted]	[redacted]
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	0.129 (0.107 to 0.150)	0.125 (0.103 to 0.147)
P value	-	< 0.0001	< 0.0001
Trough FEV_1 response (L), week 6, *other secondary end point*			
N[a]	[redacted]	[redacted]	[redacted]
Common baseline mean (SE)[a]	[redacted]		

Outcome	ENERGITO (1237.11)		
	TIO/OLO 5/5 mcg (n = 221)	FP/SAL 500/50 mcg (n = 219)	FP/SAL 250/50 mcg (n = 212)
Adjusted mean (SE)[b]	[redacted]	[redacted]	[redacted]
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	0.058 (0.034 to 0.082)	0.047 (0.022 to 0.071)
P value	-	< 0.0001[c]	0.0002
Harms			
AEs, n (%)	75 (33.9)	81 (37.0)	63 (29.7)
SAEs, n (%)	7 (3.2)	9 (4.1)	4 (1.9)
WDAEs, n (%)	6 (2.7)	3 (1.4)	2 (0.9)
Notable harms, n (%)			
Cardiac disorders	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]

AE = adverse event; AUC = area under the curve; CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FP = fluticasone propionate; MD = mean difference; OLO = olodaterol; SAE = serious adverse event; SAL = salmeterol; SE = standard error; TIO = tiotropium; vs. = versus; WDAE = withdrawal due to adverse event.

[a] Number of patients contributing to MMRM; baseline mean calculated from all patients contributing to MMRM.

[b] MMRM with treatment and period as fixed effects, patient as random effect, patient baseline and period baseline as covariates, and compound symmetry as a covariance structure for within-patient variation.

[c] No control for statistical testing outside the testing hierarchy.

Source: Clinical Study Report.[9]

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.[10,11] Pathological changes in the lung vary between individuals, but usually involve a combination of airway inflammation (chronic bronchitis) and parenchymal destruction (emphysema).[12] There is significant overlap of COPD subtypes, with many individuals presenting with features of both chronic bronchitis and emphysema.[11] The nature of symptomatic impairment may vary from patient to patient; however, cough, excess sputum production, and dyspnea are the typical symptoms of COPD. COPD is largely caused by smoking and it is often associated with multiple comorbid conditions (e.g., diabetes, ischemic heart disease, muscle wasting, bone loss, anemia, cancer, anxiety, and depression).[11]

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.[13] By 2020, COPD is projected to become the third leading cause of death worldwide.[13] According to a 2009 Statistics Canada report, COPD affects 4% of the Canadian population ≥ 35 years of age.[14] Among COPD patients in Canada aged 35 to 79 years, 7% had stage II (moderate) or higher COPD.[15] COPD is associated with high rates of admissions and readmissions to hospital (i.e., of all COPD patients hospitalized in 2006-2007, 18% were readmitted once and 14% were readmitted twice).[16] 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 a year.[17]

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 after a full inspiration with no limit to duration of expiration. A post-bronchodilator FEV_1/FVC ratio < 0.7 indicates airway obstruction. The Canadian Thoracic Society classification of COPD severity is summarized in Table 7.

TABLE 7: CANADIAN THORACIC SOCIETY CLASSIFICATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE SEVERITY BY SYMPTOMS, DISABILITY, AND IMPAIRMENT OF LUNG FUNCTION

COPD Stage	Spirometry (Post-bronchodilator)[a]	Symptoms
I: Mild	$FEV_1 \geq 80\%$ predicted, $FEV_1/FVC < 0.7$	Shortness of breath from COPD[b] 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[b] causing the patient to stop after walking approximately 12 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[b] 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-sided heart failure
IV: Very severe	$FEV_1 < 30\%$ predicted, $FEV_1/FVC < 0.7$	NA

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; NA = not available.
[a] Post-bronchodilator FEV_1 to FVC ratio < 0.7 is required to establish the diagnosis of COPD.
[b] In the presence of non-COPD conditions that may cause shortness of breath (e.g., cardiac dysfunction, anemia, muscle weakness, metabolic disorders), symptoms may not appropriately reflect COPD disease severity. Classification of COPD severity should be undertaken with care in patients with comorbid diseases or other possible contributors to shortness of breath.
Source: O'Donnell et al., 2007.[10]

1.2 Standards of Therapy

The goals of COPD management are to prevent disease progression, reduce frequency and severity of exacerbations, alleviate symptoms, improve exercise tolerance and daily activity, treat exacerbations and complications, improve health status, and reduce mortality.[10] 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.[11] Regular exercise with cardiorespiratory conditioning can improve functional status and sensation of dyspnea in COPD patients, more so than use of medications alone.

Bronchodilators form the mainstay of pharmacotherapy for COPD[11] and include short-acting $beta_2$ agonists such as salbutamol and short-acting muscarinic antagonists such as ipratropium. Long-acting $beta_2$ agonists (LABAs) such as salmeterol, formoterol, and indacaterol or long-acting muscarinic antagonists (LAMA) such as tiotropium, aclidinium, and glycopyrronium, as well as combinations of fixed-dose LABAs and inhaled corticosteroids (ICS) (i.e., LABA/ICS) 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. Inhaled corticosteroids 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.[18-20] There may also be a subpopulation of COPD patients who have concomitant asthma or airway eosinophilia where ICS use may be beneficial.[21-23] Phosphodiesterase inhibitors (theophylline and, more recently, roflumilast) are adjunctive therapies for COPD management that may be more effective in

patients with demonstrable neutrophilic airway inflammation. Inhaled medications are most commonly delivered as pressurized metered dose inhalers 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.[11]

1.3 Drug

Tiotropium bromide monohydrate/olodaterol hydrochloride (TIO/OLO, Inspiolto Respimat) is a long-acting muscarinic antagonist/long-acting beta$_2$ agonist (LAMA/LABA) fixed-dose combination formulation. Stimulation of beta$_2$ receptors has a bronchodilator effect on the lungs, as does blockade of muscarinic M3 receptors, thus the combination of these two drugs exerts a dual bronchodilator effect. TIO/OLO is indicated for the long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema. It is not indicated for the relief of acute deterioration of COPD or asthma. The fixed-dose combination is available as a solution for oral inhalation using the Respimat inhaler, with each actuation delivering TIO/OLO at a dose of 2.5/2.5 mcg. The recommended dose for TIO/OLO is 5/5 mcg once daily, given as two inhalations from the Respimat inhaler at the same time of day.

Indication under review
For the long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema.
Listing criteria requested by sponsor
For the long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema, if the following clinical criteria are met: • moderate to severe COPD as defined by spirometry; • inadequate response to a LABA or LAMA.

TABLE 8: KEY CHARACTERISTICS OF TIOTROPIUM/OLODATEROL, ACLIDINIUM/FORMOTEROL, UMECLIDINIUM/ VILANTEROL, AND GLYCOPYRRONIUM/INDACATEROL

	Tiotropium/ Olodaterol	Aclidinium/ Formoterol	Umeclidinium/ Vilanterol	Glycopyrronium/ Indacaterol
Mechanism of Action	Tiotropium blocks muscarinic M3 receptors. M3 receptors in lungs mediate bronchoconstriction, so blockade of these receptors leads to bronchodilation. Olodaterol stimulates beta$_2$ receptors in the lungs. Beta$_2$ receptors mediate bronchodilation, so stimulation of these receptors leads to bronchodilation.	Aclidinium blocks muscarinic M3 receptors. M3 receptors in lungs mediate bronchoconstriction, so blockade of these receptors leads to bronchodilation. Formoterol stimulates beta$_2$ receptors in the lungs. Beta$_2$ receptors mediate bronchodilation, so stimulation of these receptors leads to bronchodilation.	Umeclidinium blocks muscarinic M3 receptors. M3 receptors in lungs mediate bronchoconstriction, so blockade of these receptors leads to bronchodilation. Vilanterol stimulates beta$_2$ receptors in the lungs. Beta$_2$ receptors mediate bronchodilation, so stimulation of these receptors leads to bronchodilation.	Glycopyrronium blocks muscarinic M3 receptors. M3 receptors in lungs mediate bronchoconstriction, so blockade of these receptors leads to bronchodilation. Indacaterol stimulates beta$_2$ receptors in the lungs. Beta$_2$ receptors mediate bronchodilation, so stimulation of these receptors leads to bronchodilation.
Indication[a]	Long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD including chronic bronchitis and emphysema	Long-term maintenance bronchodilator treatment of airflow obstruction and relief of symptoms in 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	Long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD including chronic bronchitis and emphysema
Route of Administration	Oral inhalation of a soft mist (2.5 mcg tiotropium and 2.5 mcg olodaterol per actuation) using the Respimat device	Oral inhalation of dry powder (400 mcg aclidinium and 12 mcg formoterol) using the Genuair device	Oral inhalation of dry powder (62.5 mcg umeclidinium and 25 mcg vilanterol) using the Ellipta device	Oral inhalation of dry powder (110 mcg indacaterol and 50 mcg glycopyrronium) using the Breezhaler device
Recommended Dose	Tiotropium/olodaterol 5/5 mcg once daily	Aclidinium/formoterol 400/12 mcg twice daily (once in morning, once in evening)	Umeclidinium/vilanterol 62.5/25 mcg once daily	Indacaterol/glycopyrronium 110/50 mcg once daily

	Tiotropium/ Olodaterol	Aclidinium/ Formoterol	Umeclidinium/ Vilanterol	Glycopyrronium/ Indacaterol
Serious Side Effects or Safety Issues	Anticholinergic adverse effects (dry mouth, urinary retention, aggravation of glaucoma), cardiovascular, pneumonia	Anticholinergic adverse effects (dry mouth, urinary retention, aggravation of glaucoma), cardiovascular, pneumonia	Anticholinergic adverse effects (dry mouth, urinary retention, aggravation of glaucoma), cardiovascular, pneumonia	Anticholinergic adverse effects (dry mouth, urinary retention, aggravation of glaucoma), cardiovascular, pneumonia

COPD = chronic obstructive pulmonary disease.
[a] Health Canada indication.
Source: Product monographs for Inspiolto Respimat,[24] Duaklir Genuair,[25] Anoro Ellipta,[26] and Ultibro Breezhaler.[27]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of TIO/OLO (Inspiolto Respimat) for the long-term bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase 3 studies were selected for inclusion based on the selection criteria presented in Table 9.

TABLE 9: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult patients (≥ 18 years) diagnosed with COPD, including chronic bronchitis and emphysema **Subgroups:** Age, sex, BMI, COPD severity, chronic bronchitis, emphysema, smoking status, concomitant COPD medication use, bronchodilator reversibility
Intervention	Tiotropium bromide monohydrate 2.5 mg and olodaterol hydrochloride 2.5 mcg (Inspiolto Respimat) as two inhalations once daily via the Respimat soft mist inhaler
Comparators	The following comparators used alone or in combination (as appropriate): • LABA (e.g., formoterol, indacaterol, olodaterol, salmeterol, vilanterol) • SABA (e.g., salbutamol, albuterol, levalbuterol) • LAMA (e.g., aclidinium, glycopyrronium, tiotropium, umeclidinium) • SAMA (e.g., ipratropium) • 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, emergency room visits) • COPD exacerbations • Pulmonary function tests (e.g., spirometry, FEV_1, inspiratory capacity) • Symptoms (including dyspnea) • Health-related quality of life with a validated measure (e.g., SGRQ) • Exercise tolerance

	Other efficacy outcomes: • Use of rescue medication • Patient adherence and satisfaction • Days of missed work or school **Harms outcomes:** AEs , SAEs, WDAEs, AEs of interest (e.g., CV-related, pneumonia, anticholinergic)
Study Design	Published and unpublished Phase 3 RCTs

AE = adverse event; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LABA = long-acting $beta_2$ agonist; LAMA = long-acting muscarinic antagonist; PDE4 = phosphodiesterase 4; 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–) with in-process records and daily updates via Ovid; Embase (1974–) 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 concept was Inspiolto Respimat (tiotropium and olodaterol).

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on July 3, 2015. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on November 18, 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 CADTH Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Databases (free), Internet Search, and Open Access Journals. 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 CADTH Common Drug Review (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 10; no studies were excluded.

3. RESULTS

3.1 Findings From the Literature

A total of 10 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 2 and described in Section 3.2. No reports were excluded.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

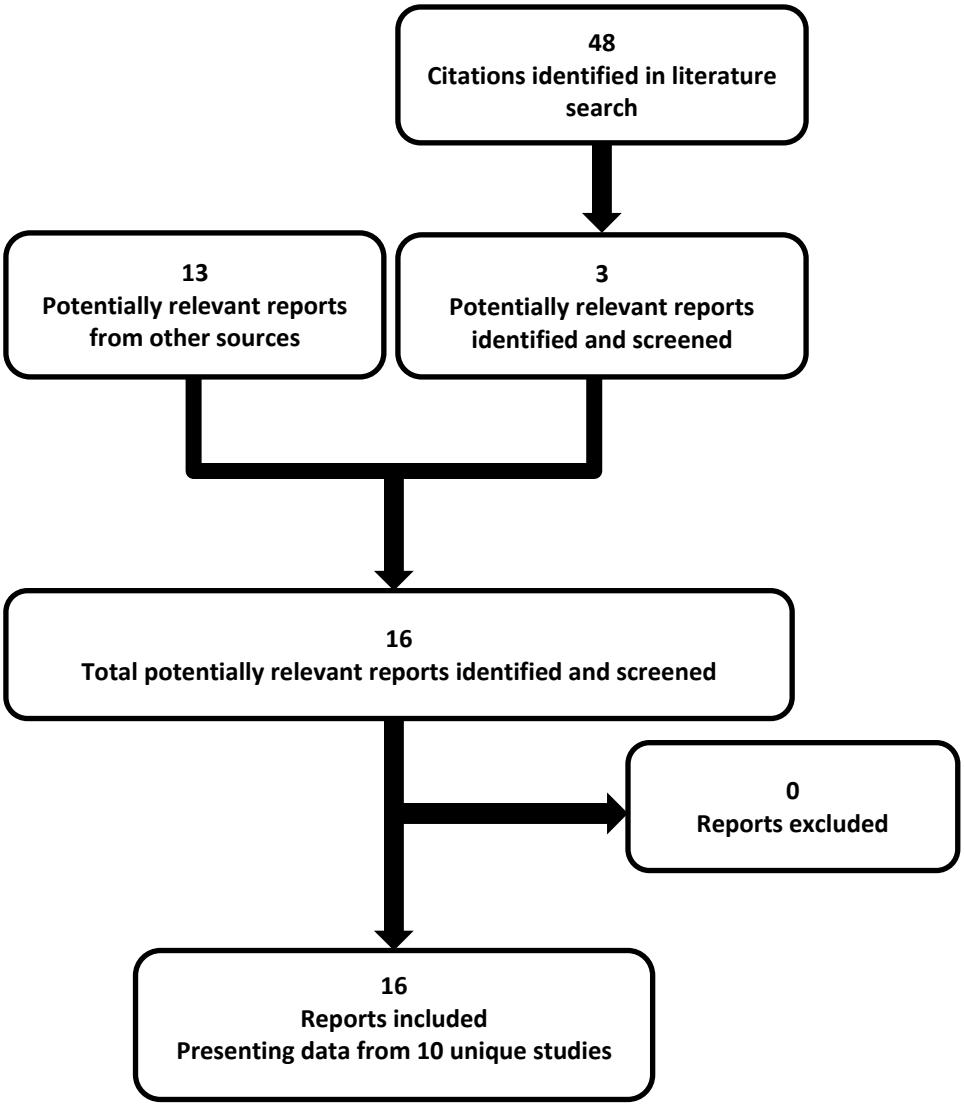

TABLE 10: DETAILS OF INCLUDED 52-WEEK PARALLEL-GROUP STUDIES

		TONADO 1 1237.5	TONADO 2 1237.6	1237.22
DESIGNS AND POPULATIONS	**Study Design**	DB RCT		
	Locations	239 centres in 25 countries (10 centres in Canada)	241 centres in 24 countries (11 centres in Canada)	24 centres in Japan
	Randomized (N)	2,624	2,539	122
	Inclusion Criteria	Adults ≥ 40 years with COPD (post-bronchodilator FEV_1 < 80% of predicted normal and FEV_1/FVC < 70% at visit 1) with moderate to very severe pulmonary impairment (GOLD stage II to stage IV), current or ex-smokers (> 10 pack-years)		
	Exclusion Criteria	History of asthma, cystic fibrosis, life-threatening pulmonary obstruction, myocardial infarction, cardiac arrhythmia, heart failure, or significant disease other than COPD		
DRUGS	**Intervention**	TIO/OLO 5/5 mcg (2 × 2.5/2.5 mcg inhalations) or 2.5/5 mcg (2 × 1.25/2.5 mcg inhalations) once daily via the Respimat inhaler		
	Comparators	TIO 2.5 mcg (2 × 1.25 mcg inhalations) TIO 5 mcg (2 × 2.5 mcg inhalations) OLO 5 mcg (2 × 2.5 mcg inhalations) All once daily via the Respimat inhaler		OLO 5 mcg (2 × 2.5 mcg inhalations) once daily via the Respimat inhaler
DURATION	**Phase**			
	Run-in	2 weeks		2 to 4 weeks
	Double-blind	52 weeks		
	Follow-up	3 weeks		
OUTCOMES	**Primary End Points**	For individual trials: • FEV_1 $AUC_{0–3h}$ on day 169 (week 24) • Trough FEV_1 on day 170 (week 24) For pooled analysis: • SGRQ total score on day 169 (week 24)		Safety (defined post hoc as number of patients with drug-related adverse events)
	Other End Points	For individual trials: • TDI focal score • SGRQ total score • Use of rescue medication For pooled analysis: • FEV_1 $AUC_{0–12h}$ • TDI focal score • COPD exacerbations		• FEV_1 $AUC_{0–3h}$ • Trough FEV_1 • Use of rescue medication
NOTES	**Publications**	Buhl et al. 2015[28] Ferguson et al. 2015[29] (post-hoc analysis)		None

AUC = area under the curve; COPD = chronic obstructive pulmonary disease; DB = double-blind; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Lung Disease; OLO = olodaterol; RCT = randomized controlled trial; SGRQ = St. George's Respiratory Questionnaire; TDI = transition dyspnea index; TIO = tiotropium.

Note: Two additional reports were included.[30,31]

Source: Clinical Study Reports.[1,2,32]

TABLE 11: DETAILS OF INCLUDED 12-WEEK PHASE 3B STUDIES

		OTEMTO 1 1237.25	OTEMTO 2 1237.26
DESIGNS AND POPULATIONS	**Study Design**	DB RCT	
	Locations	77 centres in 10 countries	78 centres in 11 countries
	Randomized (N)	812	809
	Inclusion Criteria	Adults ≥ 40 years with COPD (post-bronchodilator 30% ≤ FEV_1 < 80% of predicted normal, FEV_1/FVC < 70% at visit 1) with moderate to severe pulmonary impairment (GOLD stage II to stage III), current or ex-smokers (> 10 pack-years)	
	Exclusion Criteria	History of asthma, cystic fibrosis, life-threatening pulmonary obstruction, myocardial infarction, cardiac arrhythmia, heart failure, or significant disease other than COPD	
DRUGS	**Intervention**	TIO/OLO 5/5 mcg (2 × 2.5/2.5 mcg inhalations) once daily via the Respimat inhaler	
	Comparators	TIO 5 mcg (2 × 2.5 mcg inhalations) Placebo All once daily via the Respimat inhaler	
DURATION	**Phase**		
	Run-in	2 weeks	
	Double-blind	12 weeks	
	Follow-up	3 weeks	
OUTCOMES	**Primary End Points**	• FEV_1 $AUC_{0–3h}$ • Trough FEV_1 • SGRQ total score (individual and combined trial data)	
	Other End Points	• TDI focal score • Use of rescue medication	
NOTES	**Publications**	Singh et al. 2015[33]	

AUC = area under the curve; COPD = chronic obstructive pulmonary disease; DB = double-blind; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Lung Disease; OLO = olodaterol; RCT = randomized controlled trial; SGRQ = St. George's Respiratory Questionnaire; TDI = transition dyspnea index; TIO = tiotropium.
Note: Two additional reports were included.[30,31]
Source: Clinical Study Reports.[3,4]

TABLE 12: DETAILS OF INCLUDED STUDY: SIX-WEEK LUNG FUNCTION PROFILE CROSSOVER STUDY (VIVACITO)

		VIVACITO 1237.20
DESIGNS AND POPULATIONS	**Study Design**	DB RCT (incomplete crossover)
	Locations	29 centres in 7 countries: Belgium, Canada (4), Denmark, Germany, Hungary, Netherlands, US
	Randomized (N)	219
	Inclusion Criteria	Adults ≥ 40 years with COPD (post-bronchodilator FEV_1 < 80% of predicted normal and FEV_1/FVC < 70% at visit 1) with moderate to very severe pulmonary impairment (GOLD stage II to stage IV), current or ex-smokers (> 10 pack-years)
	Exclusion Criteria	History of asthma, cystic fibrosis, life-threatening pulmonary obstruction, myocardial infarction, cardiac arrhythmia, heart failure, or significant disease other than COPD
DRUGS	**Intervention**	TIO/OLO 5/5 mcg (2 × 2.5/2.5 mcg inhalations) or 2.5/5 mcg (2 × 1.25/2.5 mcg inhalations) once daily via the Respimat inhaler
	Comparators	TIO 2.5 mcg (2 × 1.25 mcg inhalations) TIO 5 mcg (2 × 2.5 mcg inhalations) OLO 5 mcg (2 × 2.5 mcg inhalations) Placebo All once daily via the Respimat inhaler
DURATION	**Phase**	
	Run-in	2 to 6 weeks
	Double-blind	6 weeks treatment, 3 weeks washout (4 treatments)
	Follow-up	3 weeks
OUTCOMES	**Primary End Point**	FEV_1 $AUC_{0–24h}$
	Other End Points	• FEV_1 $AUC_{0–12h}$ • FEV_1 $AUC_{12–24h}$ • Trough FEV_1
NOTES	**Publications**	Beeh et al. 2015[34]

AUC = area under the curve; COPD = chronic obstructive pulmonary disease; DB = double-blind; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Lung Disease; OLO = olodaterol; RCT = randomized controlled trial; TIO = tiotropium.
Note: Two additional reports were included.[30,31]
Source: Clinical Study Reports.[5]

TABLE 13: DETAILS OF INCLUDED EXERCISE TOLERANCE STUDIES

		MORACTO 1 1237.13	MORACTO 2 1237.14	TORRACTO 1237.15
DESIGNS AND POPULATIONS	**Study Design**	DB RCT (incomplete crossover)		DB RCT
	Locations	43 centres in 10 countries: Argentina, Australia, Austria, Belgium, Canada (3), Chile, Germany, Italy, New Zealand, US	33 centres in 8 countries: Argentina, Austria, Canada (4), Germany, Netherlands, Russia, Sweden, US	58 centres in 10 countries: Argentina, Canada (5), Finland, France, Germany, Hungary, Italy, Spain, UK, US
	Randomized (N)	295	291	404
	Inclusion Criteria	Adults between 40 and 75 years with COPD (post-bronchodilator 30% ≤ FEV_1 < 80% of predicted normal and FEV_1/FVC < 70% at visit 1) with moderate to severe pulmonary impairment (GOLD stage II to stage III), current or ex-smokers (> 10 pack-years)		
	Exclusion Criteria	• History of asthma, cystic fibrosis, life-threatening pulmonary obstruction, myocardial infarction, cardiac arrhythmia, heart failure, or significant disease other than COPD • Patients with a limitation of exercise performance as a result of factors other than fatigue or exertional dyspnea • Patients with an endurance time ≥ 25 min during training or at baseline • Patients with an endurance time ≥ 15 min during training or at baseline were excluded from the ESWT (TORRACTO)		
DRUGS	**Intervention**	TIO/OLO 5/5 mcg (2 × 2.5/2.5 mcg inhalations) or 2.5/5 mcg (2 × 1.25/2.5 mcg inhalations) once daily via the Respimat inhaler		
	Comparators	TIO 5 mcg (2 × 2.5 mcg inhalations) OLO 5 mcg (2 × 2.5 mcg inhalations) Placebo All once daily via the Respimat inhaler		Placebo
DURATION	**Phase**			
	Run-in	2 weeks		3 weeks
	Double-blind	6 weeks treatment, 3 weeks washout (4 treatments)		12 weeks
	Follow-up	3 weeks		3 weeks
OUTCOMES	**Primary End Points**	• IC at rest before CWRCE to symptom limitation at 75% maximal work capacity[a] after 6 weeks • EET during CWRCE to symptom limitation at 75% maximal work capacity[a] after 6 weeks		EET during CWRCE to symptom limitation at 75% maximal work capacity[a] after 12 weeks
	Other End Points	• Slope of the intensity of breathing discomfort during CWRCE • FEV_1 (one hour post-dose) after 6 weeks • Trough FEV_1 after 6 weeks • IC during CWRCE • Intensity of breathing discomfort (Borg scale)		• EET during the ESWT to symptom limitation at walking speed corresponding to 85% of predicted maximal oxygen consumption after 12 weeks • IC at rest and during CWRCE • Trough FEV_1

		MORACTO 1 1237.13	MORACTO 2 1237.14	TORRACTO 1237.15
NOTES	**Publications**	None	None	None

COPD = chronic obstructive pulmonary disease; CWRCE = constant work rate cycle ergometry; DB = double-blind; EET = exercise endurance time; ESWT = endurance shuttle walk test; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Lung Disease; IC = inspiratory capacity; OLO = olodaterol; RCT = randomized controlled trial; TIO = tiotropium.

[a] Maximal work capacity was defined as the maximum work rate achieved for at least 30 seconds during the incremental cycle ergometry performed at visit 1.

Note: Two additional reports were included.[30,31]

Source: Clinical Study Reports.[6-8]

TABLE 14: DETAILS OF INCLUDED STUDY: SIX-WEEK TIOTROPIUM/OLODATEROL VERSUS FLUTICASONE PROPIONATE/SALMETEROL CROSSOVER STUDY (ENERGITO)

		ENERGITO 1237.11
DESIGNS AND POPULATIONS	**Study Design**	DB DD RCT (complete crossover)
	Locations	29 centres in 8 countries
	Randomized (N)	229
	Inclusion Criteria	Adults ≥ 40 years with COPD (post-bronchodilator 30% ≤ FEV_1 < 80% of predicted normal and FEV_1/FVC < 70% at visit 1) with moderate to severe pulmonary impairment (GOLD stage II to stage III), current or ex-smokers (> 10 pack-years)
	Exclusion Criteria	History of asthma, cystic fibrosis, life-threatening pulmonary obstruction, myocardial infarction, cardiac arrhythmia, heart failure, or significant disease other than COPD
DRUGS	**Intervention**	TIO/OLO 5/5 mcg (2 × 2.5/2.5 mcg inhalations) or 2.5/5 mcg (2 × 1.25/2.5 mcg inhalations) once daily via the Respimat inhaler
	Comparators	FP/SAL 250/50 mcg FP/SAL 500/50 mcg Twice daily dry powder inhalation via the Accuhaler
DURATION	**Phase**	
	Run-in	4 weeks
	Double-blind	6 weeks treatment, 3 weeks washout
	Follow-up	3 weeks
OUTCOMES	**Primary End Point**	FEV_1 $AUC_{0–12h}$ after 6 weeks
	Other End Points	• FEV_1 $AUC_{0–24h}$ after 6 weeks • FEV_1 $AUC_{12–24h}$ after 6 weeks • Trough FEV_1 after 6 weeks
NOTES	**Publications**	None

AUC = area under the curve; COPD = chronic obstructive pulmonary disease; DB = double-blind; DD = double dummy; FEV_1 = forced expiratory volume in 1 second; FP = fluticasone propionate; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Lung Disease; OLO = olodaterol; RCT = randomized controlled trial; SAL = salmeterol; TIO = tiotropium.
Note: Two additional reports were included.[30,31]
Source: Clinical Study Reports.[9]

3.2 Included Studies

3.2.1 Description of studies

Ten superiority studies met the inclusion criteria for the systematic review (Table 10, Table 11, Table 12, Table 13, and Table 14). All of the studies were phase 3, multi-centre, multinational (except Study 1237.22), double-blind randomized controlled trials conducted in patients with moderate to severe COPD that included TIO/OLO 5/5 mcg fixed-dose combination delivered via the Respimat device as an intervention. All of the studies except for the two phase 3b studies (OTEMTO 1 and OTEMTO 2) also included TIO/OLO 2.5/5 mcg as an intervention. All of the studies included a three-week follow-up period after the last dose of treatment.

TONADO 1 (N = 2,624) and TONADO 2 (N = 2,539) were multinational, 52-week, parallel-group randomized controlled trials evaluating the efficacy and safety of TIO/OLO compared with its individual

components: TIO 5 mcg, TIO 2.5 mg, and OLO 5 mcg. OTEMTO 1 (N = 812) and OTEMTO 2 (N = 809) were 12-week, phase 3b, parallel-group, randomized controlled trials evaluating the efficacy and safety of TIO/OLO 5/5 mcg compared with TIO 5 mcg and placebo.

Study 1237.22 (N = 122) was a 52-week, parallel-group, safety and efficacy study conducted in Japan comparing TIO/OLO with OLO 5 mcg that was conducted to meet Japanese regulatory requirements. The study sample size (< 40 patients per group) was too small to draw valid conclusions, the primary end point of drug-related adverse events (AEs) was defined post hoc, and the population was solely Japanese patients, limiting the generalizability of this study. Due to the number of important methodological issues with this study, the details are limited to presentation in Section 3.1 and Section 3.2.1 of this report.

VIVACITO (N = 219) was a six-treatment, four-period, incomplete crossover study evaluating the 24-hour lung function profiles of TIO/OLO compared with its individual components and placebo. In VIVACITO, patients were treated after a two- to six-week run-in period with four of the six treatments, six weeks each with a three-week washout period between each treatment. Each patient was assigned to one of 30 treatment sequences, with each sequence consisting of four treatments in predefined order.

Three exercise tolerance studies were included in the review (MORACTO 1, MORACTO 2, and TORRACTO). MORACTO 1 (N = 295) and MORACTO 2 (N = 291) were five-treatment, four-period, incomplete crossover studies comparing TIO/OLO with TIO 5 mcg, OLO 5 mcg, and placebo. In MORACTO 1 and MORACTO 2, patients were treated after a two-week run-in period with four of the five treatments, six weeks each with a three-week washout period between each treatment. Each patient was assigned to one of five treatment sequences. TORRACTO (N = 404) was a 12-week, parallel-group, randomized controlled trial comparing TIO/OLO with placebo, where patients were treated after a three-week run-in period.

ENERGITO (N = 229) was a double-blind, double-dummy, complete crossover randomized controlled trial evaluating the efficacy and safety of TIO/OLO compared with the ICS/LABA combination fluticasone propionate/salmeterol (FP/SAL) at doses of 500/50 mcg and 250/50 mcg delivered via the Accuhaler. Patients were treated after a four-week run-in period with all four treatments, six weeks each with a three-week washout period between each treatment.

Only results of Health Canada–approved doses of TIO/OLO, TIO, and OLO are presented in this report. Results from the TIO/OLO 2.5/5 mcg and tiotropium 2.5 mcg groups that were included in the studies are not presented in this review.

3.2.2 Populations

a) Inclusion and exclusion criteria

The inclusion criteria were similar across studies, including patients with moderate to severe COPD at least 40 years of age who were current or ex-smokers. In the exercise tolerance studies (MORACTO 1, MORACTO 2, and TORRACTO), only patients between 40 and 75 years of age were included. In OTEMTO 1 and OTEMTO 2, the exercise tolerance studies, and ENERGITO, patients were required to have a post-bronchodilator $FEV_1 \geq 30\%$ and < 80% of predicted normal, as opposed to just < 80% of predicted normal in the other studies. In addition, patients enrolled in these studies were restricted to Global Initiative for Chronic Lung Disease (GOLD) stage II to stage III (moderate to severe COPD), while patients with GOLD stage II to stage IV (moderate to very severe COPD) were enrolled in TONADO 1, TONADO 2, and VIVACITO. Exclusion criteria were also similar across studies, with patients having a

history of asthma, cystic fibrosis, cardiovascular disorders, or other significant diseases other than COPD. In the exercise tolerance studies, patients with a limitation of exercise performance as a result of factors other than fatigue or exertional dyspnea were also excluded. In addition, patients with an exercise endurance time (EET) of at least 25 minutes during training or baseline were excluded from the exercise tolerance studies, and patients with an EET of at least 15 minutes were excluded from the endurance shuttle walk test in TORRACTO.

b) Baseline characteristics

Demographic and baseline characteristics of the included studies are summarized in Table 15, Table 17, Table 18, and Table 19. Almost all the patients (> 92%) enrolled in the studies were Caucasian, except in TONADO 1 and TONADO 2, where < 65% of patients were Caucasian and approximately 25% of patients were Asian. In TONADO 1 and TONADO 2, there was a higher proportion of patients categorized as GOLD stage IV (very severe) disease (about 12%) compared with the other studies, which was reflective of the inclusion criteria. The enrolment of more patients with very severe COPD in TONADO 1 and TONADO 2 was also reflected in slightly lower mean FEV_1/FVC values and a slightly higher proportion of patients who were hospitalized for a COPD exacerbation in the preceding 12 months. The age range of patients enrolled in the exercise endurance studies (MORACTO 1, MORACTO 2, TORRACTO) and VIVACITO was 40 to 78 years, while the age range of patients enrolled in the other studies was 40 to 89 years. In the TIO 5 mcg group of TONADO 2, there were patients up to 97 years of age. Overall, baseline characteristics were similar between treatment groups within the studies.

Baseline medication use is summarized in Table 20. Overall, medication use was balanced between treatment groups in the parallel-group studies. In TONADO 1, baseline medication use was slightly higher in the TIO/OLO 5/5 mcg group compared with the monotherapy groups.

TABLE 15: SUMMARY OF BASELINE CHARACTERISTICS OF INCLUDED 52-WEEK PARALLEL-GROUP STUDIES

Characteristic	TONADO 1 (1237.5)			TONADO 2 (1237.6)		
	TIO/OLO 5/5 mcg (N = 522)	TIO 5 mcg (N = 527)	OLO 5 mcg (N = 528)	TIO/OLO 5/5 mcg (N = 507)	TIO 5 mcg (N = 506)	OLO 5 mcg (N = 510)
Demographics						
Age, mean years (SD)	64.8 (8.2)	64.2 (8.5)	63.7 (8.0)	62.7 (8.4)	63.5 (8.7)	64.7 (8.3)
Age, range	42 to 85	40 to 89	40 to 86	40 to 82	40 to 97	43 to 87
Male, n (%)	384 (73.6)	383 (72.7)	386 (73.1)	349 (68.8)	372 (73.5)	378 (74.1)
Caucasian, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Former smoker, n (%)	333 (63.8)	339 (64.3)	332 (62.9)	296 (58.4)	324 (64.0)	328 (64.3)
Current smoker, n (%)	189 (36.2)	188 (35.7)	196 (37.1)	211 (41.6)	182 (36.0)	182 (35.7)
Pack-years, mean (SD)	47.4 (26.1)	47.1 (28.7)	46.4 (23.3)	46.0 (25.0)	45.5 (26.5)	47.8 (27.0)
COPD disease characteristics						
Duration, mean years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	TONADO 1 (1237.5)			TONADO 2 (1237.6)		
	TIO/OLO 5/5 mcg (N = 522)	TIO 5 mcg (N = 527)	OLO 5 mcg (N = 528)	TIO/OLO 5/5 mcg (N = 507)	TIO 5 mcg (N = 506)	OLO 5 mcg (N = 510)
(SD) [range]						
Emphysema, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic bronchitis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COPD exacerbations in last 12 months requiring hospitalization, n (%)						
1	24 (4.6)	23 (4.4)	13 (2.5)	23 (4.5)	22 (4.3)	14 (2.7)
2	2 (0.4)	5 (0.9)	3 (0.6)	3 (0.6)	4 (0.8)	2 (0.4)
> 2	2 (0.4)	1 (0.2)	3 (0.6)	1 (0.2)	2 (0.4)	1 (0.2)
COPD severity (GOLD), n (%)						
Stage II (moderate)	258 (49.4)	263 (49.9)	257 (48.7)	244 (48.1)	254 (50.2)	275 (53.9)
Stage III (severe)	201 (38.5)	202 (38.3)	207 (39.2)	207 (40.8)	185 (36.6)	171 (33.5)
Stage IV (very severe)	63 (12.1)	62 (11.8)	64 (12.1)	56 (11.0)	66 (13.0)	64 (12.5)
Lung function						
Pre-bronchodilator FEV_1 (L), mean (SD)	1.167 (0.473)	1.197 (0.495)	1.204 (0.515)	1.193 (0.513)	1.203 (0.514)	1.215 (0.495)
Post-salbutamol FEV_1 (L), mean (SD)	1.334 (0.488)	1.362 (0.510)	1.371 (0.527)	1.355 (0.523)	1.379 (0.533)	1.383 (0.512)
Pre-bronchodilator FEV_1/FVC, mean (SD)	42.907 (11.537)	43.377 (11.727)	43.180 (11.567)	44.823 (11.586)	44.239 (12.359)	44.480 (11.589)
Post-salbutamol FEV_1/FVC (L), mean (SD)	44.175 (11.610)	44.739 (11.729)	44.414 (11.495)	46.100 (11.584)	45.290 (12.323)	45.660 (11.609)
ICS use						
ICS use at baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Lung Disease; ICS = inhaled corticosteroid; OLO = olodaterol; SD = standard deviation; TIO = tiotropium.

[a] Specific to an Asian population.

[b] Number of patients who used pulmonary medication within the last three months before visit 0.

Source: Clinical Study Reports.[1,2,32]

TABLE 16: SUMMARY OF BASELINE CHARACTERISTICS OF INCLUDED 12-WEEK PHASE 3B STUDIES

Characteristic	OTEMTO 1 (1237.25)			OTEMTO 2 (1237.26)		
	TIO/OLO 5/5 mcg (N = 203)	TIO 5 mcg (N = 203)	Placebo (N = 204)	TIO/OLO 5/5 mcg (N = 202)	TIO 5 mcg (N = 203)	Placebo (N = 202)
Demographics						
Age, mean years (SD)	64.7 (8.9)	64.9 (8.2)	65.1 (8.3)	65.2 (8.5)	64.7 (8.4)	64.0 (8.3)
Age, range	47 to 87	46 to 87	41 to 89	45 to 85	41 to 85	42 to 89
Male, n (%)	114 (56.2)	124 (61.1)	127 (62.3)	133 (65.8)	130 (64.0)	117 (57.9)
Caucasian, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Smoking history						
Former smoker, n (%)	92 (45.3)	105 (51.7)	116 (56.9)	110 (54.5)	112 (55.2)	107 (53.0)
Current smoker, n (%)	111 (54.7)	98 (48.3)	88 (43.1)	92 (45.5)	91 (44.8)	95 (47.0)
Pack-years, mean (SD)	48.5 (23.2)	50.4 (26.3)	49.2 (27.3)	48.7 (23.5)	48.1 (25.4)	50.7 (26.3)
COPD disease characteristics						
Duration, mean years (SD) [range]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Emphysema, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chronic bronchitis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COPD exacerbations in last 12 months requiring hospitalization, n (%)						
1	2 (1.0)	2 (1.0)	0	3 (1.5)	6 (3.0)	3 (1.5)
2	0	0	1 (0.5)	1 (0.5)	0	0
> 2	0	0	0	0	0	0
COPD severity (GOLD), n (%)						
Stage II (moderate)	130 (64.0)	127 (62.6)	140 (68.6)	125 (61.9)	137 (67.5)	122 (60.4)
Stage III (severe)	73 (36.0)	73 (36.0)	63 (30.9)	77 (38.1)	66 (32.5)	79 (39.1)
Stage IV (very severe)	0	2 (1.0)	1 (0.5)	0	0	1 (0.5)
Lung function						
Pre-bronchodilator FEV_1 (L), mean (SD)	1.315 (0.491)	1.306 (0.458)	1.383 (0.527)	1.358 (0.467)	1.403 (0.511)	1.333 (0.493)

Characteristic	OTEMTO 1 (1237.25)			OTEMTO 2 (1237.26)		
	TIO/OLO 5/5 mcg (N = 203)	TIO 5 mcg (N = 203)	Placebo (N = 204)	TIO/OLO 5/5 mcg (N = 202)	TIO 5 mcg (N = 203)	Placebo (N = 202)
Post-salbutamol FEV_1 (L), mean (SD)	1.502 (0.502)	1.494 (0.471)	1.578 (0.539)	1.566 (0.482)	1.585 (0.514)	1.530 (0.527)
Pre-bronchodilator FEV_1/FVC, mean (SD)	47.201 (10.461)	47.748 (10.304)	47.431 (11.009)	48.725 (10.202)	50.366 (10.925)	48.558 (10.596)
Post-salbutamol FEV_1/FVC (L), mean (SD)	48.985 (10.324)	49.623 (10.461)	49.661 (10.890)	50.905 (10.032)	52.436 (10.737)	50.217 (10.546)
ICS use						
ICS use at baseline, n (%)	85 (41.9)	77 (37.9)	71 (34.8)	72 (35.6)	71 (35.0)	71 (35.1)

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Lung Disease; ICS = inhaled corticosteroid; OLO = olodaterol; SD = standard deviation; TIO = tiotropium.
Source: Clinical Study Reports.[3,4]

TABLE 17: SUMMARY OF BASELINE CHARACTERISTICS OF INCLUDED STUDY: SIX-WEEK LUNG FUNCTION PROFILE CROSSOVER STUDY (VIVACITO)

Characteristic	VIVACITO (1237.20)
	Treated (N = 219)
Demographics	
Age, mean years (SD)	61.1 (7.7)
Age, range	41 to 78
Male, n (%)	129 (58.9)
Caucasian, n (%)	[redacted]
Smoking history	
Former smoker, n (%)	82 (37.4)
Current smoker, n (%)	137 (62.6)
Pack-years, mean (SD)	[redacted]
COPD disease characteristics	
Duration, mean years (SD) [range]	[redacted]
Emphysema, n (%)	[redacted]
Chronic bronchitis, n (%)	[redacted]
COPD exacerbations in last 12 months requiring hospitalization, n (%)	
1	[redacted]
COPD severity (GOLD), n (%)	
Stage II (moderate)	139 (63.5)
Stage III (severe)	75 (34.2)
Stage IV (very severe)	5 (2.3)
Lung function	
Pre-bronchodilator FEV_1 (L), mean (SD)	1.361 (0.471)
Post-salbutamol FEV_1 (L), mean (SD)	1.553 (0.487)
Pre-bronchodilator FEV_1/FVC, mean (SD)	45.779 (10.829)
Post-salbutamol FEV_1/FVC (L), mean (SD)	47.955 (10.880)
ICS use	
ICS use at baseline, n (%)	90 (41.1)

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Lung Disease; ICS = inhaled corticosteroid; OLO = olodaterol; SD = standard deviation; TIO = tiotropium.
Source: Clinical Study Report.[5]

TABLE 18: SUMMARY OF BASELINE CHARACTERISTICS OF INCLUDED EXERCISE TOLERANCE STUDIES

Characteristic	MORACTO 1 (1237.13)	MORACTO 2 (1237.14)	TORRACTO (1237.15)	
	Treated (N = 295)	Treated (N = 291)	TIO/OLO 5/5 mcg (N = 139)	Placebo (N = 132)
Demographics				
Age, mean years (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Age, range	[redacted]	[redacted]	[redacted]	[redacted]

Characteristic	MORACTO 1 (1237.13)	MORACTO 2 (1237.14)	TORRACTO (1237.15)	
	Treated (N = 295)	Treated (N = 291)	TIO/OLO 5/5 mcg (N = 139)	Placebo (N = 132)
Male, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Caucasian, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Smoking history				
Former smoker, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Current smoker, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Pack-years, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
COPD disease characteristics				
Duration, mean years (SD) [range]	[redacted]	[redacted]	[redacted]	[redacted]
Emphysema, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Chronic bronchitis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
COPD exacerbations in last 12 months requiring hospitalization, n (%)				
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
> 2	[redacted]	[redacted]	[redacted]	[redacted]
COPD severity (GOLD), n (%)				
Stage II (moderate)	[redacted]	[redacted]	[redacted]	[redacted]
Stage III (severe)	[redacted]	[redacted]	[redacted]	[redacted]
Stage IV (very severe)	[redacted]	[redacted]	[redacted]	[redacted]
Lung function				
Pre-bronchodilator FEV_1 (L), mean (SD)	1.540 (0.492)	1.560 (0.503)	1.460 (0.476)	1.501 (0.507)
Post-salbutamol FEV_1 (L), mean (SD)	1.713 (0.483)	1.728 (0.512)	1.659 (0.504)	1.695 (0.522)
Pre-bronchodilator FEV_1/FVC, mean (SD)	50.866 (10.958)	49.270 (10.574)	50.335 (10.954)	50.811 (10.590)

Characteristic	MORACTO 1 (1237.13)	MORACTO 2 (1237.14)	TORRACTO (1237.15)	
	Treated (N = 295)	Treated (N = 291)	TIO/OLO 5/5 mcg (N = 139)	Placebo (N = 132)
Post-salbutamol FEV_1/FVC (L), mean (SD)	52.479 (10.834)	50.827 (10.522)	51.923 (10.745)	52.506 (10.005)
ICS use				
ICS use at baseline, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Lung Disease; ICS = inhaled corticosteroid; OLO = olodaterol; SD = standard deviation; TIO = tiotropium.
Source: Clinical Study Reports.[6-8]

TABLE 19: SUMMARY OF BASELINE CHARACTERISTICS OF INCLUDED STUDY: SIX-WEEK TIOTROPIUM/OLODATEROL VERSUS FLUTICASONE PROPIONATE/SALMETEROL CROSSOVER STUDY (ENERGITO)

Characteristic	ENERGITO (1237.11)
	Treated (N = 229)
Demographics	
Age, mean years (SD)	63.6 (7.6)
Age, range	45 to 84
Male, n (%)	148 (64.6)
Caucasian, n (%)	228 (99.6)
Smoking history	
Former smoker, n (%)	127 (55.5)
Current smoker, n (%)	102 (44.5)
Pack-years, mean (SD)	39.1 (18.3)
COPD disease characteristics	
Duration, mean years (SD) [range]	[redacted]
Emphysema, n (%)	[redacted]
Chronic bronchitis, n (%)	[redacted]
COPD exacerbations in last 12 months requiring hospitalization, n (%)	
1	[redacted]
COPD severity (GOLD), n (%)	
Stage II (moderate)	165 (72.1)
Stage III (severe)	64 (27.9)
Lung function	
Pre-bronchodilator FEV_1 (L), mean (SD)	1.425 (0.456)
Post-salbutamol FEV_1 (L), mean (SD)	1.624 (0.468)
Pre-bronchodilator FEV_1/FVC, mean (SD)	[redacted]

Characteristic	ENERGITO (1237.11)
	Treated (N = 229)
Post-salbutamol FEV_1/FVC (L), mean (SD)	[redacted]
ICS use	
ICS use at baseline, n (%)	109 (47.6)

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Lung Disease; ICS = inhaled corticosteroid; OLO = olodaterol; SD = standard deviation; TIO = tiotropium.
Source: Clinical Study Report.[9]

TABLE 20: SUMMARY OF BASELINE CHRONIC OBSTRUCTIVE PULMONARY DISEASE MEDICATION USE

	Baseline COPD Medications, n (%)					
Study and Treatment	Any	ICS	LABA	LAMA	SABA	SAMA
TONADO 1 (1237.5)						
TIO/OLO 5/5 mcg (N = 522)	429 (82.2)	270 (51.7)	261 (50.0)	210 (40.2)	223 (42.7)	52 (10.0)
TIO 5 mcg (N = 527)	411 (78.0)	237 (45.0)	234 (44.4)	173 (32.8)	208 (39.5)	60 (11.4)
OLO 5 mcg (N = 528)	419 (79.4)	249 (47.2)	249 (47.2)	185 (35.0)	223 (42.2)	50 (9.5)
TONADO 2 (1237.6)						
TIO/OLO 5/5 mcg (N = 507)	391 (77.1)	236 (46.5)	225 (44.4)	168 (33.1)	177 (34.9)	73 (14.4)
TIO 5 mcg (N = 506)	390 (77.1)	229 (45.3)	216 (42.7)	173 (34.2)	193 (38.1)	71 (14.0)
OLO 5 mcg (N = 510)	418 (82.0)	256 (50.2)	242 (47.5)	180 (35.3)	201 (39.4)	84 (16.5)
OTEMTO 1 (1237.25)						
TIO/OLO 5/5 mcg (N = 203)	162 (79.8)	85 (41.9)	73 (36.0)	77 (37.9)	100 (49.3)	20 (9.9)
TIO 5 mcg (N = 203)	160 (78.8)	77 (37.9)	78 (38.4)	64 (31.5)	112 (55.2)	18 (8.9)
Placebo (N = 204)	156 (76.5)	71 (34.8)	78 (38.2)	83 (40.7)	101 (49.5)	13 (6.4)
OTEMTO 2 (1237.26)						
TIO/OLO 5/5 mcg (N = 202)	142 (70.3)	72 (35.6)	82 (40.6)	70 (34.7)	93 (46.0)	9 (4.5)
TIO 5 mcg (N = 203)	158 (77.8)	71 (35.0)	81 (39.9)	77 (37.9)	109 (53.7)	15 (7.4)
Placebo (N = 202)	156 (77.2)	71 (35.1)	76 (37.6)	59 (29.2)	107 (53.0)	16 (7.9)
VIVACITO (1237.20)						
Treated (N = 219)	182 (83.1)	90 (41.1)	99 (45.2)	88 (40.2)	133 (60.7)	17 (7.8)
MORACTO 1 (1237.13)						
Treated (N = 295)	[redacted]					
MORACTO 2 (1237.14)						
Treated (N = 291)	[redacted]					
TORRACTO (1237.15)						
TIO/OLO 5/5 mcg (N = 139)	[redacted]					
Placebo (N = 132)						
ENERGITO (1237.11)						
Treated (N = 229)	209 (93.3)	109 (47.6)	140 (61.1)	123 (53.7)	122 (53.3)	24 (10.5)

ICS = inhaled corticosteroids; LABA = long-acting $beta_2$ adrenergic; LAMA = long-acting muscarinic antagonists; OLO = olodaterol; SABA = short-acting $beta_2$ agonist; SAMA = short-acting muscarinic antagonists; SD = standard deviation; TIO = tiotropium.
[a]Taken within the last three months before visit 0.
Source: Clinical Study Reports.[1-9,32]

3.2.3 Interventions

Medication was delivered via the Respimat soft mist inhaler as two inhalations given at the same time once daily in the morning. Each newly assembled Respimat inhaler had to be primed by actuating until aerosol was visible followed by three additional actuations. Respimat inhalers dispensed during the treatment period could be used for approximately 30 days each, and patients were to return all used and unused test medication at each clinic visit. Detailed written instructions and training for the use of the inhaler were given to the patient at visit 1, which included inhalation from a training device. These instructions were repeated at the first visit of each treatment period for crossover studies and at subsequent visits for other studies, though without inhalation from a training device. During the treatment phase at each clinic visit, study medication was self-administered by the patient under direct supervision of the investigating physician or study personnel.

In ENERGITO, FP/SAL was administered via the Accuhaler twice daily, once in the morning and once in the evening. The Accuhaler did not require priming and was used for 30 days of treatment at a time. Once assembled, the Respimat device had a shelf-life of three months, while the Accuhaler had no shelf-life restriction. A double-dummy design was employed in ENERGITO, where patients were given both Respimat and Accuhaler devices during each treatment phase and were to administer two inhalations in the morning from the Respimat device, and one inhalation in the morning and evening from the Accuhaler device (Table 21).

TABLE 21: TREATMENTS ADMINISTERED IN THE ENERGITO STUDY

Treatment Group	Morning Dose	Evening Dose
TIO/OLO 2.5/5 mcg	2 inhalations Respimat: TIO/OLO 1.25/2.5 mcg 1 inhalation Accuhaler: placebo FP/SAL	1 inhalation Accuhaler: placebo FP/SAL
TIO/OLO 5/5 mcg	2 inhalations Respimat: TIO/OLO 2.5/2.5 mcg 1 inhalation Accuhaler: placebo FP/SAL	1 inhalation Accuhaler: placebo FP/SAL
FP/SAL 250/50 mcg	2 inhalations Respimat: placebo TIO/OLO 1 inhalation Accuhaler: FP/SAL 250/50 mcg	1 inhalation Accuhaler: FP/SAL 250/50 mcg
FP/SAL 500/50 mcg	2 inhalations Respimat: placebo TIO/OLO 1 inhalation Accuhaler: FP/SAL 500/50 mcg	1 inhalation Accuhaler: FP/SAL 500/50 mcg

FP = fluticasone propionate; OLO = olodaterol; SAL = salmeterol; TIO = tiotropium.
Source: Clinical Study Report.[9]

Patients, investigators, and personnel involved in analyzing data were to remain blinded with regard to randomized treatment assignments until after database lock. All trials were designed to include a run-in period ranging from two to six weeks, a double-blind treatment period lasting 52 weeks (TONADO 1 and TONADO 2), 12 weeks (OTEMTO 1, OTEMTO 2, and TORRACTO), or six weeks with a three-week washout period between each treatment (VIVACITO, MORACTO 1, MORACTO 2, and ENERGITO), and a follow-up period of three weeks. ICSs were permitted during the study provided the patient was on a stable dose for six weeks prior to study entry. LABAs and LAMAs other than the trial medication had to be washed out prior to visit 1. Short-acting beta$_2$ agonists were provided as rescue medication, with an eight-hour washout prior to pulmonary function tests. Short-acting muscarinic antagonists required an eight-hour washout prior to visit 1.

Only treatment groups that consisted of Health Canada–approved regimens are summarized in this report (Table 22). As such, the results for TIO/OLO 2.5/5 mcg in all of the included studies and the

results for TIO 2.5 mcg (lower than the Health Canada–recommended dose) in TONADO 1, TONADO 2, and VIVACITO are excluded from this report.

TABLE 22: TREATMENT GROUPS INCLUDED OR EXCLUDED FOR THE INCLUDED STUDIES

	Included						Excluded	
Study	**TIO/OLO 5/5 mcg**	**TIO 5 mcg**	**OLO 5 mcg**	**Placebo**	**FP/SAL 500/ 50 mcg**	**FP/SAL 250/ 50 mcg**	**TIO/OLO 2.5/ 5 mcg[a]**	**TIO 2.5 mcg[a]**
TONADO 1 (1237.5)	x	x	x	NA	NA	NA	x	x
TONADO 2 (1237.6)	x	x	x	NA	NA	NA	x	x
VIVACITO (1237.20)	x	x	x	x	NA	NA	x	x
MORACTO 1 (1237.13)	x	x	x	x	NA	NA	x	NA
MORACTO 2 (1237.14)	x	x	x	x	NA	NA	x	NA
TORRACTO (1237.15)	x	NA	NA	x	NA	NA	x	NA
OTEMTO 1 (1237.25)	x	x	NA	x	NA	NA	NA	NA
OTEMTO 2 (1237.26)	x	x	NA	x	NA	NA	NA	NA
ENERGITO (1237.11)	x	NA	NA	NA	x	x	x	NA

FP = fluticasone propionate; NA = not available; OLO = olodaterol; SAL = salmeterol; TIO = tiotropium; x = treatment group included in the respective study.
[a] Excluded because dose not approved by Health Canada.
Source: Clinical Study Reports.[1-9,32]

Concomitant medication allowed included inhaled salbutamol as a study-provided relief medication, but an eight-hour washout was required prior to pulmonary function tests. Patients were also allowed to continue using their ICS if they were taking it prior to study entry in all studies except ENERGITO, provided it was maintained at a consistent dose and stabilized over six weeks. If patients switched from LABA/ICS combination to ICS monotherapy, this must have happened at least 48 hours prior to the start of the study. Mucolytics, medications for rhinitis, antibiotics for acute infections, short-term oxygen use, ongoing use of systemic beta-blockers, localized corticosteroid injections, and cautious use of oral muscarinic antagonists were also allowed.

3.2.4 Outcomes

a) Pulmonary function

FEV_1 is the volume of air after a full inspiration that can be forcibly expired in one second. A change of 0.10 to 0.14 L versus placebo is a generally accepted minimal clinically important difference (MCID) for FEV_1 (see APPENDIX 4: VALIDITY OF OUTCOME MEASURES). Trough FEV_1 is the FEV_1 value at the end of the dosing interval (24 hours). In TONADO 1, TONADO 2, OTEMTO 1, OTEMTO 2, VIVACITO, and ENERGITO, this was calculated as the mean of two FEV_1 measurements performed at 23 hours and 23 hours 50 minutes after inhalation of study medication at the clinic visit on the previous day. In the

exercise tolerance studies, trough FEV_1 was measured 30 minutes before dosing. Trough FEV_1 response was defined as the change from baseline in trough FEV_1 at the end of the dosing interval. Trough FEV_1 response was a co-primary end point in TONADO 1, TONADO 2, OTEMTO 1, and OTEMTO 2.

The efficacy outcomes in the trials included the normalized area under the curve (AUC) for FEV_1 over three hours (TONADO 1, TONADO 2, OTEMTO 1, and OTEMTO 2), 12 hours (VIVACITO, ENERGITO), or 24 hours (VIVACITO, ENERGITO) measured at the end of treatment or at defined points during the treatment period. The FEV_1 AUC value was calculated using the trapezoidal method, divided by the duration in hours and reported in litres. The FEV_1 AUC response was defined as the FEV_1 AUC value minus baseline FEV_1.

b) Exercise endurance time

EET is a measure of exercise endurance and was assessed in two ways in the included exercise endurance studies. In all of the exercise endurance studies (MORACTO 1, MORACTO 2, and TORRACTO), EET was assessed during constant work rate cycle ergometry (CWRCE) at the end of the treatment period as a primary end point. A maximal work capacity was determined for each patient at visit 1 and was defined as the maximum work rate achieved for at least 30 seconds during incremental cycle ergometry, where increasing loads are applied to the cycle as the patient pedals at a constant frequency until the patient stops from exhaustion. The EET during CWRCE was determined at subsequent visits and defined as the time to symptom limitation (i.e., unwilling to continue exercising because of discomfort) at 75% maximal work capacity. Patients with an EET ≥ 25 minutes during CWRCE at training or baseline were not eligible for randomization in the exercise endurance studies.

In TORRACTO, the EET was also assessed for the endurance shuttle walking test (ESWT) at selected centres with suitable infrastructure and qualified personnel to conduct the test. A maximal exercise capacity was determined at visit 1 through an incremental shuttle walk test, where the patient was to walk/jog/run up and down a 10-metre course at a speed dictated by an audio signal until he or she was limited by symptoms or unable to maintain the instructed walking pace. The EET during ESWT at the end of treatment was a secondary end point and defined as the time to symptom limitation at a walking speed corresponding to 85% of the predicted maximal oxygen consumption as determined by a table developed by a research group that links distances covered during the incremental shuttle walk test to the speed corresponding to 85% of predicted maximal oxygen consumption. The patient was to walk at this speed until he or she was limited by symptoms or unable to maintain the walking pace. Patients with an EET ≥ 15 minutes during the ESWT at training or baseline were not eligible for randomization in this study.

In all of the exercise endurance studies, the CWRCE and ESWT were performed two hours after inhalation of study medication. There are no widely accepted MCIDs for EET (see APPENDIX 4: VALIDITY OF OUTCOME MEASURES).

c) Lung volume

Inspiratory capacity at rest before cycle ergometry was measured as a primary end point in MORACTO 1 and MORACTO 2 and as a secondary end point in TORRACTO. The patient was to breathe through a mouthpiece attached to the breathing circuit of the metabolic cart and, after three minutes of breathing in a relaxed manner, was asked to take a deep breath in. At least three reproducible inspiratory capacity measurements were obtained before taking the mean of the two highest reproducible efforts. For inspiratory capacity during CWRCE, measurements were taken at two-minute intervals in a similar manner to measurements taken at rest. Inspiratory capacity measures taken at the end of exercise were performed within 15 seconds after exercise.

d) Measures of Dyspnea

The transition dyspnea index (TDI) is used to measure the severity of dyspnea relative to a patient's baseline state (baseline dyspnea index) according to 24 items in three categories: functional impairment, magnitude of task and magnitude of effort. At baseline, a category is graded from 0 (severe) to 4 (unimpairment), and the scores from the categories are added to form the baseline focal score (range 0 to 12). The TDI ranges from −3 (major deterioration) to +3 (major improvement) for each category. The TDIs for the three categories are added to obtain a focal score (range −9 to +9). Higher scores indicate greater improvements from baseline, and a one-unit change in TDI is considered to be an appropriate MCID (see APPENDIX 4: VALIDITY OF OUTCOME MEASURES). TDI focal score was a secondary end point in OTEMTO 1 and OTEMTO 2 (week 12), and a secondary end point in a pre-specified pooled analysis of TONADO 1 and TONADO 2.

In the exercise endurance studies (MORACTO 1, MORACTO 2, and TORRACTO), the slope of the intensity of breathing discomfort during CWRCE to symptom limitation at 75% maximal work capacity at the end of treatment was a secondary end point. The intensity of breathing discomfort was measured using the modified Borg scale, which is a categorical scale from 0 (normal breathing) to 10 (maximum dyspnea). Patients were measured prior to exercise, at two-minute intervals during exercise, and within 15 seconds of the end of exercise. The slope was defined as the intensity of breathing discomfort at end-exercise minus the intensity of breathing discomfort at rest divided by endurance time.

e) Quality of life

The St. George's Respiratory Questionnaire (SGRQ) is a quality-of-life measure that was developed to measure impaired health and perceived well-being for patients with chronic airflow limitation. SGRQ consists of 50 items (with 76 weighted responses) covering 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. A decrease in score indicates an improvement in health-related quality of life, and a decrease of four units in the total score is considered to be an appropriate MCID (see APPENDIX 4: VALIDITY OF OUTCOME MEASURES). SGRQ was assessed as an exploratory efficacy outcome in TONADO 1 and TONADO 2, as a primary outcome in OTEMTO 1 and OTEMTO 2, and as a primary outcome in a pre-specified pooled analysis of TONADO 1 and TONADO 2.

f) Rescue salbutamol use

Use of rescue medication was defined as the number of puffs used in the previous 24 hours for as-needed relief of the symptoms of COPD. It was a daily patient self-reported measure using a paper or electronic diary, which was reviewed by the investigator at each visit. Rescue salbutamol use was

evaluated as an additional end point in TONADO 1, TONADO 2, OTEMTO 1, and OTEMTO 2 as the weekly mean number of puffs used per day over the entire treatment period.

g) COPD exacerbations

A COPD exacerbation was defined as a complex of lower respiratory events or symptoms (at least two of the following: shortness of breath, sputum production, purulent sputum, cough, wheezing, chest tightness) related to COPD, lasting at least three days, that required a change in treatment (use of antibiotics, systemic steroids, emergency treatment, or hospitalization) beyond the study drug or rescue salbutamol. Exacerbations were classified as follows depending on the requirement for medication or hospitalization: mild (a new prescription of maintenance bronchodilator only), moderate (antibiotics and/or systemic steroids without hospitalization), or severe (hospitalization). COPD exacerbations were monitored and recorded as part of the AE reporting process. COPD exacerbations were assessed as an additional efficacy end point in the pre-specified pooled analysis of TONADO 1 and TONADO 2 and were reported in the safety analyses in the other included studies.

h) Patient adherence

In TONADO 1, TONADO 2, OTEMTO 1, OTEMTO 2, VIVACITO, and ENERGITO, compliance was assessed using electronic or paper diary data recording whether or not patients took their daily doses of study medication. In VIVACITO and ENERGITO, diary data were compared with the dose counters of the Respimat and Accuhaler (ENERGITO) devices for a plausibility check. In the exercise tolerance studies (MORACTO 1, MORACTO 2, and TORRACTO), compliance was assessed by reviewing the dose counter on the Respimat device.

i) Harms

AEs and serious adverse events (SAEs) were assessed in all studies. The detection, documentation, and reporting of AEs and SAEs were the responsibility of the investigator or site staff. All AEs and SAEs were collected, documented, and reported to the sponsor by the investigator from the time of signing the informed consent onward throughout the treatment period and the three-week follow-up period after last administration of study medication. A treatment-emergent AE was defined as any event or worsening event with an onset any time following the first dose of study drug up to three weeks after the last study drug intake. An AE could include an exacerbation of a condition, the emergence of a new condition, or signs, symptoms, or clinical sequelae of a suspected interaction or overdose of any treatment (study-related or concomitant). An SAE could include any unexpected medical occurrence that resulted in death, was considered life-threatening, or resulted in disability or hospitalization.

3.2.5 Statistical analysis

a) Sample size calculations

All of the included trials were powered to detect differences in the primary outcomes between the TIO/OLO fixed-dose combination and the individual TIO and OLO components and placebo (for the trials that included a placebo group), or FP/SAL (ENERGITO).

TONADO 1 and TONADO 2 were powered to detect differences between the TIO/OLO fixed-dose combination and the individual TIO and OLO components in trough FEV_1 and FEV_1 $AUC_{0–3h}$ at week 24. Patient dropout at 24 weeks was expected to be low, therefore sample size inflation was not considered in the calculations. Using a one-sided significance level of 2.5%, a sample size of 500 patients per group provided 90% power to detect a difference of 0.046 L in trough FEV_1 and 0.046 L in FEV_1 $AUC_{0–3h}$. Standard deviations (SDs) used for the calculations (0.226 L for FEV_1 $AUC_{0–3h}$; 0.225 L for trough FEV_1) were based on four previous studies. A similar analysis with similar assumptions was

performed in OTEMTO 1 and OTEMTO 2. Using a two-sided significance level of 5%, a sample size of 200 patients per group provided 90% power to detect a difference of 0.073L in FEV_1 $AUC_{0–3h}$ and trough FEV_1 and 87% power to detect a difference of 4 units in SGRQ total score assuming an SD of 14 units.

In VIVACITO, a sample size of 180 patients per group provided 90% power to detect a treatment difference of 60 mL for FEV_1 $AUC_{0–24h}$ between TIO/OLO fixed-dose combination and the individual TIO and OLO components and placebo. An additional 36 patients were added to cover for estimated dropout, resulting in a sample size of 216 randomized patients. A residual SD of 190 mL was used for the calculations using data from four previous trials.

MORACTO 1 and MORACTO 2 were powered to test for differences in the co-primary end points, EET and inspiratory capacity, between TIO/OLO fixed-dose combination and the individual TIO and OLO components and placebo. Sample size calculations were based on an estimated treatment difference of 10% (SD 0.181 seconds) for EET and 0.1 L (SD 0.42 L) for inspiratory capacity. Using a two-sided significance level of 5%, a sample size of 203 patients provided 90% power to detect a difference in EET and inspiratory capacity. However, since these studies were incomplete crossover designs, a complete crossover sample size was multiplied by 4/3 and rounded up to the nearest multiple of 10, giving a required sample size of 280 patients.

In TORRACTO, an SD for log_{10} endurance time from CWRCE of 0.206 was taken from a previous trial. Since dropout at 12 weeks was expected to be low and the repeated measures model used accounted for missing values, sample size inflation was not considered for the calculations. Based on a one-sided significance level of 2.5%, a sample size of 130 patients per group provided 90% power to detect a 21% improvement in EET during CWRCE at 75% maximal work capacity. For the key secondary end point of EET during ESWT, historical data from a single-centre trial were used to estimate a delta (SD) of 128 (141) seconds. A sample size of 50 patients per group provided 90% power to detect a difference of 100 seconds with an SD of 150 seconds, which was considered to be sufficient for the subgroup of patients participating in the ESWT.

In ENERGITO, an estimate of the expected SD for FEV_1 $AUC_{0–12h}$ was determined from three previous studies to be 206 mL. Using a two-sided significance level of 5%, a sample size of 181 completed patients provided 90% power to detect a treatment difference of 50 mL for FEV_1 $AUC_{0–12h}$. Assuming an estimated dropout rate of 20%, 228 patients were planned for randomization.

b) Data handling

The primary outcomes for the included studies were assessed using the full analysis set and a restricted maximum likelihood–based mixed model for repeated measures analysis. In the parallel-group studies (TONADO 1, TONADO 2, OTEMTO 1, OTEMTO 2, and TORRACTO), the mixed model for repeated measures included treatment, test day, and treatment-by-test day interaction as fixed, categorical effects; baseline and baseline-by-test day interaction were included as continuous fixed covariates; and patient was included as a random effect. In the crossover studies (VIVACITO, MORACTO 1, MORACTO 2, and ENERGITO), the mixed model for repeated measures included treatment and period as fixed effects; study baseline (MORACTO 1 and MORACTO 2) or period baseline and patient baseline (VIVACITO and ENERGITO) as continuous fixed covariates; and patient as a random effect. If the number of patients in the per-protocol set was < 90% of the number of patients in the full analysis set, the primary analysis was to be repeated using the per-protocol set and presented as a supportive analysis. The secondary efficacy analyses for the included studies were analyzed in the same manner as the primary efficacy

analyses. Missing data at a given visit were imputed by the available data from the patient at that visit and completely missing visits were handled through the statistical model.

In the parallel-group studies (TONADO 1, TONADO 2, OTEMTO 1, OTEMTO 2, and TORRACTO), a sensitivity analysis was conducted using the empirical "sandwich" estimator approach to calculate a variance-covariance matrix of the fixed-effects parameters. In TONADO 1 and TONADO 2, an additional pattern mixture model was applied. In the crossover studies (VIVACITO, MORACTO 1, MORACTO 2, and ENERGITO), a sensitivity analysis considering patients as fixed effects was implemented (study baseline was not included as a covariate in the sensitivity analysis model).

c) Multiplicity

A step-down closed testing procedure was used to control for multiple statistical testing in nine of the included studies (Table 23). Each test was considered confirmatory if all previous tests were significant at the two-sided 5% level and the treatment effect favoured TIO/OLO fixed-dose combination. Otherwise, the test was considered exploratory only.

TABLE 23: CONTROL FOR MULTIPLE STATISTICAL TESTING IN THE INCLUDED STUDIES

Study	End Point(s)	Step-Down Closed Testing Statistical Hierarchy
TONADO 1 **TONADO 2**	Primary: FEV_1 $AUC_{0–3h}$ Trough FEV_1	TIO/OLO 5/5 mcg vs. OLO 5 mcg for FEV_1 $AUC_{0–3h}$ TIO/OLO 5/5 mcg vs. TIO 5 mcg for FEV_1 $AUC_{0–3h}$ TIO/OLO 5/5 mcg vs. OLO 5 mcg for trough FEV_1 TIO/OLO 5/5 mcg vs. TIO 5 mcg for trough FEV_1 TIO/OLO 2.5/5 mcg vs. OLO 5 mcg for FEV_1 $AUC_{0–3h}$ TIO/OLO 2.5/5 mcg vs. TIO 2.5 mcg for FEV_1 $AUC_{0–3h}$ TIO/OLO 2.5/5 mcg vs. OLO 5 mcg for trough FEV_1 TIO/OLO 2.5/5 mcg vs. TIO 2.5 mcg for trough FEV_1
OTEMTO 1 **OTEMTO 2**	Primary: FEV_1 $AUC_{0–3h}$ Trough FEV_1 SGRQ total score	TIO/OLO 5/5 mcg vs. placebo for FEV_1 $AUC_{0–3h}$ TIO/OLO 5/5 mcg vs. placebo for trough FEV_1 TIO/OLO 2.5/5 mcg vs. placebo for FEV_1 $AUC_{0–3h}$ TIO/OLO 2.5/5 mcg vs. placebo for trough FEV_1 TIO/OLO 5/5 mcg vs. placebo for SGRQ total score (combined data) TIO/OLO 5/5 mcg vs. placebo for SGRQ total score TIO/OLO 2.5/5 mcg vs. placebo for SGRQ total score (combined data) TIO/OLO 2.5/5 mcg vs. placebo for SGRQ total score
VIVACITO	Primary: FEV_1 $AUC_{0–24h}$ Secondary: FEV_1 $AUC_{0–12h}$ FEV_1 $AUC_{12–24h}$	*FEV_1 $AUC_{0–24h}$* TIO/OLO 5/5 mcg vs. placebo TIO/OLO 5/5 mcg vs. OLO 5 mcg TIO/OLO 5/5 mcg vs. TIO 5 mcg TIO/OLO 2.5/5 mcg vs. placebo TIO/OLO 2.5/5 mcg vs. OLO 5 mcg TIO/OLO 2.5/5 mcg vs. TIO 2.5 mcg *FEV_1 $AUC_{0–12h}$* TIO/OLO 5/5 mcg vs. placebo TIO/OLO 5/5 mcg vs. OLO 5 mcg TIO/OLO 5/5 mcg vs. TIO 5 mcg TIO/OLO 2.5/5 mcg vs. placebo TIO/OLO 2.5/5 mcg vs. OLO 5 mcg TIO/OLO 2.5/5 mcg vs. TIO 2.5 mcg *FEV_1 $AUC_{12–24h}$* TIO/OLO 5/5 mcg vs. placebo

Study	End Point(s)	Step-Down Closed Testing Statistical Hierarchy
		TIO/OLO 5/5 mcg vs. OLO 5 mcg TIO/OLO 5/5 mcg vs. TIO 5 mcg TIO/OLO 2.5/5 mcg vs. placebo TIO/OLO 2.5/5 mcg vs. OLO 5 mcg TIO/OLO 2.5/5 mcg vs. TIO 2.5 mcg TIO/OLO 2.5/5 mcg vs. TIO 5 mcg
MORACTO 1 **MORACTO 2**	Primary: IC at rest EET during CWRCE	*IC at rest* TIO/OLO 5/5 mcg vs. placebo TIO/OLO 5/5 mcg vs. OLO 5 mcg TIO/OLO 5/5 mcg vs. TIO 5 mcg *EET during CWRCE* TIO/OLO 5/5 mcg vs. placebo TIO/OLO 5/5 mcg vs. OLO 5 mcg TIO/OLO 5/5 mcg vs. TIO 5 mcg *IC at rest* TIO/OLO 2.5/5 mcg vs. placebo TIO/OLO 2.5/5 mcg vs. OLO 5 mcg TIO/OLO 2.5/5 mcg vs. TIO 5 mcg *EET during CWRCE* TIO/OLO 2.5/5 mcg vs. placebo TIO/OLO 2.5/5 mcg vs. OLO 5 mcg TIO/OLO 2.5/5 mcg vs. TIO 5 mcg
TORRACTO	Primary: EET during CWRCE Key Secondary: EET during ESWT Other Secondary: IC at rest	*EET during CWRCE* TIO/OLO 5/5 mcg vs. placebo TIO/OLO 2.5/5 mcg vs. placebo *EET during ESWT* TIO/OLO 5/5 mcg vs. placebo TIO/OLO 2.5/5 mcg vs. placebo *IC at rest* TIO/OLO 5/5 mcg vs. placebo TIO/OLO 2.5/5 mcg vs. placebo
ENERGITO	Primary: FEV_1 $AUC_{0–12h}$ Key Secondary: FEV_1 $AUC_{0–24h}$	*FEV_1 $AUC_{0–12h}$* TIO/OLO 5/5 mcg vs. FP/SAL 250/50 mcg TIO/OLO 5/5 mcg vs. FP/SAL 500/50 mcg *FEV_1 $AUC_{0–24h}$* TIO/OLO 5/5 mcg vs. FP/SAL 250/50 mcg TIO/OLO 5/5 mcg vs. FP/SAL 500/50 mcg *FEV_1 $AUC_{0–12h}$* TIO/OLO 2.5/5 mcg vs. FP/SAL 250/50 mcg TIO/OLO 2.5/5 mcg vs. FP/SAL 500/50 mcg *FEV_1 $AUC_{0–24h}$* TIO/OLO 2.5/5 mcg vs. FP/SAL 250/50 mcg TIO/OLO 2.5/5 mcg vs. FP/SAL 500/50 mcg

AUC = area under the curve; CWRCE = constant work rate cycle ergometry; EET = exercise endurance time; ESWT = endurance shuttle walking test; FEV_1 = forced expiratory volume in 1 second; FP = fluticasone propionate; IC = inspiratory capacity; OLO = olodaterol; SAL = salmeterol; SGRQ = St. George's Respiratory Questionnaire; TIO = tiotropium; vs. = versus.
Source: Clinical Study Reports.[1-9,32]

d) Analysis populations

In the included trials, the following datasets were defined.

Randomized set: All patients who signed informed consent forms and were randomized, regardless of whether the patient was treated with study medication.

Treated set: All patients in the randomized set who were dispensed study medication and were documented to have taken at least one dose of study medication.

Full analysis set: All patients in the treated set who had a non-missing baseline and at least one non-missing post-baseline measurement for any primary and key secondary efficacy outcomes (TONADO 1 and TONADO 2) or for the primary efficacy end point (all other included studies). In TONADO 1 and TONADO 2, the post-baseline measurement had to be taken before or at week 24.

Per-protocol set: All patients in the full analysis set who had no important protocol violations of relevance for the efficacy analyses.

3.3 Patient Disposition

A greater proportion of patients discontinued treatment following randomization in TONADO 1 and TONADO 2 (range 10.2% to 19.2%) compared with the other studies (range 0.7% to 10.6%) due to the 52-week duration of the studies. The most common reason for study discontinuation was AEs. In TONADO 1, a greater proportion of patients discontinued from the OLO 5 mcg group (18.4%) than the TIO/OLO 5/5 mcg (10.7%) and TIO 5 mcg (13.7%) groups. Discontinuation rates were generally higher in the placebo groups compared with the other treatment groups in OTEMTO 1, OTEMTO 2, VIVACITO, and TORRACTO.

TABLE 24: PATIENT DISPOSITION — 52-WEEK PARALLEL-GROUP STUDIES (TONADO 1, TONADO 2)

	TONADO 1 (1237.5)			TONADO 2 (1237.6)		
	TIO/OLO 5/5 mcg	TIO 5 mcg	OLO 5 mcg	TIO/OLO 5/5 mcg	TIO 5 mcg	OLO 5 mcg
Screened, N	3,369			3,518		
Randomized, n	2,624			2,539		
	522	527	528	507	507	510
Treated, n (%)	522 (100.0)	527 (100.0)	528 (100.0)	507 (100.0)	506 (99.8)	510 (100.0)
Completed, n (%)	466 (89.3)	455 (86.3)	431 (81.6)	430 (84.8)	410 (81.0)	412 (80.8)
Discontinued, n (%)	56 (10.7)	72 (13.7)	97 (18.4)	77 (15.2)	96 (19.0)	98 (19.2)
Adverse event	37 (7.1)	43 (8.2)	51 (9.7)	41 (8.1)	53 (10.5)	59 (11.6)
Protocol deviation	4 (0.8)	4 (0.8)	5 (0.9)	5 (1.0)	5 (1.0)	6 (1.2)
Lost to follow-up	0	1 (0.2)	6 (1.1)	1 (0.2)	2 (0.4)	0
Withdrew consent	11 (2.1)	17 (3.2)	29 (5.5)	29 (5.7)	34 (6.7)	29 (5.7)
Other	4 (0.8)	7 (1.3)	6 (1.1)	1 (0.2)	2 (0.4)	4 (0.8)
RS, n	522	527	528	507	507	510

	TONADO 1 (1237.5)			TONADO 2 (1237.6)		
	TIO/OLO 5/5 mcg	TIO 5 mcg	OLO 5 mcg	TIO/OLO 5/5 mcg	TIO 5 mcg	OLO 5 mcg
TS, n (%)	522 (100.0)	527 (100.0)	528 (100.0)	507 (100.0)	506 (100.0)	510 (100.0)
FAS, n (%)	522 (100.0)	526 (99.8)	528 (100.0)	505 (99.6)	503 (99.4)	507 (99.4)
PP, n (%)	484 (92.7)	507 (96.2)	513 (97.2)	492 (97.0)	489 (96.6)	490 (96.1)
Safety, n (%)	522 (100.0)	527 (100.0)	528 (100.0)	507 (100.0)	506 (100.0)	510 (100.0)

FAS = full analysis set; OLO = olodaterol; PP = per-protocol; RS = randomized set; TIO = tiotropium; TS = treated set.
Note: Patients treated with TIO/OLO 2.5/5 mcg were not included in this report.
Source: Clinical Study Reports.[1,2]

TABLE 25: PATIENT DISPOSITION — 12-WEEK PHASE 3B STUDIES (OTEMTO 1, OTEMTO 2)

	OTEMTO 1 (1237.25)			OTEMTO 2 (1237.26)		
	TIO/OLO 5/5 mcg	TIO 5 mcg	Placebo	TIO/OLO 5/5 mcg	TIO 5 mcg	Placebo
Screened, N	1,054			1,107		
Randomized, n	814			809		
	204[a]	204	204	202	203	202
Treated, n (%)	203[a] (100.0)	203 (100.0)	204 (100.0)	202 (100.0)	203 (100.0)	202 (100.0)
Completed, n (%)	195 (96.1)	192 (94.6)	178 (87.3)	198 (98.0)	191 (94.1)	182 (90.1)
Discontinued, n (%)	8 (3.9)	11 (5.4)	26 (12.7)	4 (2.0)	12 (5.9)	20 (9.9)
Adverse event	3 (1.5)	3 (1.5)	13[b] (6.4)	2[c] (1.0)	7 (3.4)	10 (5.0)
Protocol deviation	2 (1.0)	4 (2.0)	2 (1.0)	0	1 (0.5)	1 (0.5)
Lost to follow-up	1 (0.5)	0	1 (0.5)	0	1 (0.5)	0
Withdrew consent	0	2 (1.0)	4 (2.0)	1 (0.5)	0	3 (1.5)
Other	2 (1.0)	2 (1.0)	0	0	0	0
RS, n	204[a]	204	204	202	203	202
TS, n (%)	203[a] (100.0)	203 (100.0)	204 (100.0)	202 (100.0)	203 (100.0)	202 (100.0)
FAS, n (%)	202 (99.5)	203 (100.0)	204 (100.0)	200 (99.0)	201 (99.0)	199 (98.5)
PP, n (%)	200 (98.5)	203 (100.0)	199 (97.5)	199 (98.5)	199 (98.0)	197 (97.5)
Safety, n (%)	203 (100.0)	203 (100.0)	204 (100.0)	202 (100.0)	203 (100.0)	202 (100.0)

AE = adverse event; CRF = case report form; FAS = full analysis set; OLO = olodaterol; PP = per-protocol; RS = randomized set; TIO = tiotropium; TS = treated set.
[a] One patient entered the study with 2 different patient numbers (5582 and 5604). This patient was counted twice in the randomized set but only once in the treated set.
[b] Two patients (5011 and 5805) in the placebo group were recorded as discontinuing study medication due to an AE on the "Termination of Trial Medication" page of the CRF). The AEs started before the patients had taken their first dose of study medication (and ended after they had started treatment).
[c] One patient (6325) in the TIO/OLO 5/5 mcg group was recorded as discontinuing study medication due to an AE (fatal myocardial infarction) on the "Termination of Trial Medication" page of the CRF. However, in agreement with the instructions in the Investigator Site File, "continued" was selected as action taken on the AE page of the CRF because in the event of death it cannot be known when and if the patient stopped taking the study medication at the time of the event.
Source: Clinical Study Reports.[3,4]

TABLE 26: PATIENT DISPOSITION — SIX-WEEK LUNG FUNCTION PROFILE CROSSOVER STUDY (VIVACITO)

	VIVACITO (1237.20)			
	TIO/OLO 5/5 mcg	TIO 5 mcg	OLO 5 mcg	Placebo
Screened, N	259			
Randomized, n	219			
	139	138	138	138
Treated, n (%)	139 (100)	138 (100)	138 (100)	138 (100)
Completed, n (%)	138 (99.3)	135 (97.8)	136 (98.6)	130 (94.2)
Discontinued, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]
Withdrew consent	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
RS, n	219			
TS, n (%)	139 (100.0)	138 (100.0)	138 (100.0)	138 (100.0)
FAS, n (%)	212 (96.8)			
PP, n (%)	208 (95.0)			
Safety, n (%)	139 (100.0)	138 (100.0)	138 (100.0)	138 (100.0)

FAS = full analysis set; OLO = olodaterol; PP = per-protocol; RS = randomized set; TIO = tiotropium; TS = treated set.
Source: Clinical Study Report.[5]

TABLE 27: PATIENT DISPOSITION — EXERCISE TOLERANCE STUDIES

	MORACTO 1 (1237.13)				MORACTO 2 (1237.14)				TORRACTO (1237.15)	
	TIO/ OLO 5/5 mcg	TIO 5 mcg	OLO 5 mcg	Placebo	TIO/ OLO 5/5 mcg	TIO 5 mcg	OLO 5 mcg	Placebo	TIO/ OLO 5/5 mcg	Placebo
Screened, N	[redacted]				[redacted]				[redacted]	
Randomized, n	295				291				404[a]	
Treated, n (%)	[redacted]				[redacted]				[redacted]	
Completed, n (%)	[redacted]				[redacted]				[redacted]	
Discontinued, n (%)	[redacted]				[redacted]				[redacted]	
Adverse event	[redacted]				[redacted]				[redacted]	
Protocol deviation	[redacted]				[redacted]				[redacted]	
Lost to follow-up	[redacted]				[redacted]				[redacted]	
Withdrew consent	[redacted]				[redacted]				[redacted]	
Other	[redacted]				[redacted]				[redacted]	

	MORACTO 1 (1237.13)				MORACTO 2 (1237.14)				TORRACTO (1237.15)	
	TIO/ OLO 5/5 mcg	TIO 5 mcg	OLO 5 mcg	Placebo	TIO/ OLO 5/5 mcg	TIO 5 mcg	OLO 5 mcg	Placebo	TIO/ OLO 5/5 mcg	Placebo
RS, n (%)										
TS, n (%)										
FAS, n (%)										
PP, n (%)										
Safety, n (%)										

FAS = full analysis set; OLO = olodaterol; PP = per-protocol; RS = randomized set; TIO = tiotropium; TS = treated set.
Note: Patients in the TIO/OLO 2.5/5 mcg group are not included in this report.
Source: Clinical Study Reports.[6-8]

TABLE 28: PATIENT DISPOSITION — SIX-WEEK TIOTROPIUM/OLODATEROL VERSUS FLUTICASONE PROPIONATE/SALMETEROL CROSSOVER STUDY (ENERGITO)

	ENERGITO (1237.11)		
	TIO/OLO 5/5 mcg	FP/SAL 500/50 mcg	FP/SAL 250/50 mcg
Screened, N			
Randomized, n	229		
	221	219	212
Treated, n (%)	221 (100.0)	219 (100.0)	212 (100.0)
Completed, n (%)			
Discontinued, n (%)			
Adverse event			
Protocol deviation			
Loss to follow-up			
Withdrew consent			
Other			
RS, n	229		
TS, n (%)	221 (100.0)	219 (100.0)	212 (100.0)
FAS, n (%)			
PP, n (%)			
Safety, n (%)	221 (100.0)	219 (100.0)	212 (100.0)

FAS = full analysis set; FP = fluticasone propionate; OLO = olodaterol; PP = per-protocol; RS = randomized set; SAL = salmeterol; TIO = tiotropium; TS = treated set.
Source: Clinical Study Report.[9]

3.4 Exposure to Study Treatments

In TONADO 1, TONADO 2, OTEMTO 1, and OTEMTO 2, patients recorded in an electronic diary whether they took their daily doses of study medication. Compliance was calculated based on whether or not study medication was taken, instead of the amount of medication taken. In the exercise tolerance

studies (MORACTO 1, MORACTO 2, and TORRACTO), compliance was measured using the medication counter on the Respimat device and calculated as a percentage of the expected number of doses to be administered for the patient in the given time. In TORRACTO, compliance was measured during visit 5 (week 6) and visit 6 (week 12), and results from week 12 are presented. In VIVACITO and ENERGITO, compliance was determined by performing a plausibility check at each visit by comparing diary data with the dose indicator of the Respimat and Accuhaler (ENERGITO) devices. Any differences that suggested incorrect use of either device were to be discussed with the patient and recorded as compliant or not compliant.

The median exposure for all included studies was generally the full treatment period of the study: 52 weeks for TONADO 1 and TONADO 2; 12 weeks for OTEMTO 1, OTEMTO 2, and TORRACTO; and 6 weeks for VIVACITO, MORACTO 1, MORACTO 2, and ENERGITO (Table 29). Compliance to treatment was generally high across all treatment groups in all studies.

For all trials, administration of LABAs, short-acting muscarinic antagonists (SAMAs), and LAMAs was not permitted. Patients who used these medications during treatment did so for only a brief period (Table 30). In all studies except ENERGITO, ICSs were permitted as background medication provided the dose was stable at baseline and throughout the treatment period. In all studies except ENERGITO, at least 40% of patients were taking ICSs as background medication.

TABLE 29: SUMMARY OF EXPOSURE AND COMPLIANCE TO TREATMENT

Study and Treatment	Duration (Days)		Compliance		
	Mean (SD)	Median (Range)	Mean % (SD)	< 80%, n (%)	80% to 100%, n (%)
TONADO 1 (1237.5) TIO/OLO 5/5 mcg (N = 522) TIO 5 mcg (N = 527) OLO 5 mcg (N = 528)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TONADO 2 (1237.6) TIO/OLO 5/5 mcg (N = 507) TIO 5 mcg (N = 506) OLO 5 mcg (N = 510)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OTEMTO 1 (1237.25) TIO/OLO 5/5 mcg (N = 203) TIO 5 mcg (N = 203) Placebo (N = 204)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OTEMTO 2 (1237.26) TIO/OLO 5/5 mcg (N = 202) TIO 5 mcg (N = 203) Placebo (N = 202)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VIVACITO (1237.20) TIO/OLO 5/5 mcg (N = 139) TIO 5 mcg (N = 138) OLO 5 mcg (N = 138) Placebo (N = 138)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MORACTO 1 (1237.13) TIO/OLO 5/5 mcg (N = 226) TIO 5 mcg (N = 226) OLO 5 mcg (N = 217)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study and Treatment	Duration (Days)		Compliance		
	Mean (SD)	Median (Range)	Mean % (SD)	< 80%, n (%)	80% to 100%, n (%)
Placebo (N = 223)	[redacted]	[redacted]		[redacted]	[redacted]
MORACTO 2 (1237.14) TIO/OLO 5/5 mcg (N = 224) TIO 5 mcg (N = 218) OLO 5 mcg (N = 218) Placebo (N = 214)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TORRACTO (1237.15) TIO/OLO 5/5 mcg (N = 139) Placebo (N = 132)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ENERGITO (1237.11) TIO/OLO 5/5 mcg (N = 221) FP/SAL 500/50 mcg (N = 219) FP/SAL 250/50 mcg (N = 212)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

FP = fluticasone propionate; OLO = olodaterol; SAL = salmeterol; SD = standard deviation; TIO = tiotropium.

TABLE 30: SUMMARY OF ON-TREATMENT CHRONIC OBSTRUCTIVE PULMONARY DISEASE CONCOMITANT MEDICATION

	On-Treatment COPD Medications, n (%)					
Study and Treatment	Any	ICS	Mucolytics	Oxygen	SAMA	SABA
TONADO 1 (1237.5) TIO/OLO 5/5 mcg (N = 522) TIO 5 mcg (N = 527) OLO 5 mcg (N = 528)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TONADO 2 (1237.6) TIO/OLO 5/5 mcg (N = 507) TIO 5 mcg (N = 506) OLO 5 mcg (N = 510)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VIVACITO (1237.20) TIO/OLO 5/5 mcg (N = 139) TIO 5 mcg (N = 138) OLO 5 mcg (N = 138) Placebo (N = 138)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MORACTO 1 (1237.13) TIO/OLO 5/5 mcg (N = 226) TIO 5 mcg (N = 227) OLO 5 mcg (N = 217) Placebo (N = 222)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MORACTO 2 (1237.14) TIO/OLO 5/5 mcg (N = 224) TIO 5 mcg (N = 218) OLO 5 mcg (N = 219) Placebo (N = 216)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	On-Treatment COPD Medications, n (%)					
Study and Treatment	**Any**	**ICS**	**Mucolytics**	**Oxygen**	**SAMA**	**SABA**
TORRACTO (1237.15) TIO/OLO 5/5 mcg (N = 139) Placebo (N = 132)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OTEMTO 1 (1237.25) TIO/OLO 5/5 mcg (N = 203) TIO 5 mcg (N = 203) Placebo (N = 204)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OTEMTO 2 (1237.26) TIO/OLO 5/5 mcg (N = 202) TIO 5 mcg (N = 203) Placebo (N = 202)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ENERGITO (1237.11) TIO/OLO 5/5 mcg (N = 221) FP/SAL 500/50 mcg (N = 219) FP/SAL 250/50 mcg (N = 212)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

COPD = chronic obstructive pulmonary disease; FP = fluticasone propionate; ICS = inhaled corticosteroids; OLO = olodaterol; SABA = short-acting beta$_2$ agonist; SAL = salmeterol; SAMA = short-acting muscarinic antagonist; TIO = tiotropium.

3.5 Critical Appraisal

3.5.1 Internal validity

- Study 1237.22 was a 52-week safety study that met the inclusion criteria for the review but is not summarized in full in this report because of a number of methodological limitations. Study 1237.22 was conducted for Japanese regulatory purposes to evaluate the long-term safety of TIO/OLO in 100 Japanese patients. Since TONADO 1 and TONADO 2 enrolled a total of 80 Japanese patients per treatment group, Study 1237.22 enrolled 40 patients per treatment group to make up the remaining numbers, accounting for dropout. No statistical calculations were performed to determine appropriate sample sizes to power the study appropriately. In addition, the definition of the primary end point was determined post hoc.
- A pre-specified statistical testing hierarchy was included for all studies, but only for a portion of the study outcomes. Therefore, the interpretation of those outcomes that were not adjusted for multiplicity should be done with caution. Furthermore, *P* values and statistical tests were presented in instances where a higher test in the hierarchy did not meet statistical significance; however, they were considered to be descriptive. Of the comparisons of interest presented in this review, the comparison between TIO/OLO 5/5 mcg and placebo for inspiratory capacity at rest before cycle ergometry in TORRACTO fell below a statistically non-significant parameter in the chain, but statistical testing was still performed even though it should have stopped.
- There was a higher rate of discontinuation in the placebo groups compared with the other treatment groups for the 12-week trials that included a placebo group (OTEMTO 1, OTEMTO 2, and TORRACTO). This unbalanced rate of discontinuations could potentially have disrupted the balance of patient characteristics from randomization and could threaten the validity of the results. A mixed model for repeated measures analysis was used for all efficacy outcomes that assumed that data were missing at random, which may not be appropriate in these studies due to the unbalanced rates of discontinuations.

- Patient disposition, baseline characteristics, concomitant therapies, and safety analyses were based on the treated set, which included all patients who took any dose of study medication. All efficacy analyses were based on the full analysis set, which included all patients who received any dose of study medication and who had a non-missing baseline and at least one non-missing post-baseline measurement. In TONADO 1 and TONADO 2, this post-baseline measurement had to be taken prior to or at week 24. None of the analyses was based on a true intention-to-treat population, though analyses were based on a population similar enough to that of an intention-to-treat to have a low probability of materially impacting the validity of the analyses and the findings of the studies.
- For the incomplete crossover studies (VIVACITO, MORACTO 1, and MORACTO 2), baseline characteristics were presented for the total treated population and not by treatment sequence, so it was unclear whether characteristics of patients randomized to each treatment sequence were balanced and what impact this would have. Washout periods of three weeks were implemented between treatments for all crossover studies, which is sufficient for the TIO/OLO 5/5 mcg, TIO 5 mcg, and OLO 5 mcg groups. However, the clinical expert consulted for this review noted that three weeks would be the minimum amount of time needed to wash out inhaled corticosteroids, as was used in the FP/SAL 500/50 mcg and FP/SAL 250/50 mcg groups in ENERGITO. Incomplete washout would have residual effects in the next treatment administered.
- For all efficacy outcomes in all included studies, a common baseline mean was calculated using the study baseline values from all patients in the full analysis set contributing to the mixed model for repeated measures analysis. It is unclear whether it was appropriate to assume a common baseline mean across treatment groups, and whether using a mean baseline value for individual treatment groups to determine change from baseline in respective outcomes would have given different results. Although baseline characteristics were generally well balanced between treatment groups, it is unclear whether the baseline scores and measures of each outcome (FEV_1 outcomes, SGRQ total score, TDI focal score, EET, inspiratory capacity) would have been balanced. However, baseline was used as a covariate in the mixed model for repeated measures analyses.

3.5.2 External validity

- According to the clinical expert consulted for this review, the baseline characteristics were reflective of patients with moderate to severe COPD. There were higher proportions of patients with Global Initiative for Chronic Lung Disease (GOLD) stage IV disease in the TONADO 1 and TONADO 2 studies due to the differing inclusion criteria, which was reflected in pulmonary function characteristics. The exercise endurance studies were limited to patients aged 40 to 75 with GOLD stage II to stage III, but the clinical expert noted that this was to exclude the most severe patients who would be unable to complete the exercise tests. Some studies had a very high proportion of males (> 70%), which may not be reflective of the current COPD population, where the proportion of women with COPD is closer to the proportion of men with COPD.
- Patients with a diagnosis of asthma were excluded from the study population; however, there is a possibility that patients with asthma were included, as bronchodilator reversibility was not an inclusion or exclusion criterion. The proportion of patients with bronchodilator reversibility at baseline was not reported in the trials.
- The duration of all studies except TONADO 1, TONADO 2, and Study 1237.22 was six or 12 weeks. According to the clinical expert consulted for this review, this is a sufficient amount of time to ascertain clinical effects in pulmonary function tests (FEV_1). However, it is uncertain whether this would be a sufficient amount of time to see a benefit in other outcomes such as SGRQ and TDI, which were primary end points in OTEMTO 1 and OTEMTO 2. Although both SGRQ and TDI were assessed in TONADO 1 and TONADO 2, results from the individual studies were not considered as primary or secondary end points (SGRQ was a primary end point for the pooled analysis). In addition, shorter

study durations may not be sufficient to assess safety outcomes of interest such as health care resource use, COPD exacerbations, and the incidence of cardiovascular AEs and pneumonia.

- All included studies compared TIO/OLO 5/5 mcg with one of more of the following: TIO 5 mcg, OLO 5 mcg, or placebo. Only the ENERGITO study included a comparison of TIO/OLO 5/5 mcg to FP/SAL, an ICS/LABA combination. There was no direct evidence for the comparative efficacy of TIO/OLO 5/5 mcg versus other Health Canada–approved LABA/LAMA combination therapies.
- Trough FEV_1 at the end of the treatment period and FEV_1 AUC as primary or co-primary end points is not particularly well correlated to symptoms that are of greatest clinical importance to patients, such as quality of life, especially when measured over shorter time frames.
- Proper use of an inhaler may be suboptimal in routine clinical practice. Careful monitoring of compliance as it occurs under ideal study conditions may not be reflective of what typically occurs in clinical practice.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 9). See APPENDIX 3: DETAILED OUTCOME DATA for detailed efficacy data.

3.6.1 Mortality

Overall, the number of deaths across all nine studies was low. There were greater numbers of deaths in the TONADO 1 and TONADO 2 studies than in the other studies due to the longer (52-week) study duration. In TONADO 1, nine deaths occurred in both the TIO/OLO 5/5 mcg (three cardiovascular-related, one COPD-related) and TIO 5 mcg (one cardiovascular-related, two COPD-related) groups, and four deaths (two cardiovascular-related, one COPD-related) occurred in the OLO 5 mcg group (Table 31). In TONADO 2, nine deaths (two cardiovascular-related, three COPD-related) occurred in the TIO/OLO 5/5 mcg group, eight deaths (one cardiovascular-related, two COPD-related) occurred in the TIO 5 mcg group, and 10 deaths (four cardiovascular-related, two COPD-related) occurred in the OLO 5 mcg group (Table 31). In OTEMTO 1, two deaths (one cardiovascular-related) occurred in the TIO/OLO 5/5 mcg group, and two cardiovascular-related deaths occurred in the TIO 5 mcg group (Table 32). In OTEMTO 2, one cardiovascular-related death occurred in the TIO/OLO 5/5 mcg group. [redacted] (Table 34). Two deaths (one cardiovascular-related) occurred in the TIO/OLO 5/5 mcg group in the ENERGITO study (Table 36). [redacted].

3.6.2 Health resource utilization

No data for days for health resource utilization were reported in the included studies.

3.6.3 Chronic obstructive pulmonary disease exacerbations

The proportion of patients experiencing any COPD exacerbation in the 52-week studies (TONADO 1 and TONADO 2) ranged from 29.0% to 35.1%; in the 12-week studies (OTEMTO 1, OTEMTO 2, and TORRACTO) ranged from 3.9% to 12.1%; and in the six-week studies (VIVACITO, MORACTO 1, MORACTO 2, and ENERGITO) ranged from 4.2% to 12.3%. The proportions were slightly higher in the placebo groups compared with the other treatment groups. The rate of COPD exacerbations requiring hospitalization (severe exacerbations) was low in all studies (range 0 to 7.3%). There were no consistent differences in COPD exacerbations between treatment groups.

COPD exacerbations were an additional efficacy outcome in the 52-week TONADO 1 and TONADO 2 studies. In TONADO 1 and TONADO 2, the annual rate of any exacerbation per patient-year was slightly lower in the TIO/OLO 5/5 mcg group (annual rate range 0.490 to 0.508 per patient-year) than in the

monotherapy groups (annual rate range 0.543 to 0.631 per patient-year) at 52 weeks, but none of these differences was statistically significant (*P* value range 0.0678 to 0.9019) (Table 31). Hazard ratios (HRs) for the time to first COPD exacerbation of any severity were also calculated. The only statistically significant difference was found between TIO/OLO 5/5 mcg and OLO 5 mcg in TONADO 2 (HR 0.7801; 95% confidence interval [CI], 0.6272 to 0.9704]. However, this analysis was outside the pre-specified statistical testing hierarchy, which may suffer from an inflated type I error rate due to multiplicity and therefore the results were considered exploratory.

3.6.4 Pulmonary function tests

a) Trough forced expiratory volume in one second

The mean response (change from baseline FEV_1) in trough FEV_1 was a co-primary outcome in TONADO 1, TONADO 2, OTEMTO 1, and OTEMTO 2; a secondary end point in ENERGITO; and an additional end point in the remaining trials. In TONADO 1 and TONADO 2, trough FEV_1 was measured as a primary end point at week 24. In the remaining trials, trough FEV_1 results at the end of the treatment period were presented. In TONADO 1 and TONADO 2, the adjusted mean trough FEV_1 response at week 24 was statistically significantly greater in the TIO/OLO 5/5 mcg group compared with the TIO 5 mcg group (TONADO 1, mean difference [MD] 0.071 L; 95% CI, 0.047 to 0.094; $P < 0.0001$; TONADO 2, MD 0.050; 95% CI, 0.024 to 0.075; $P = 0.0001$) and the OLO 5 mcg group (TONADO 1, MD 0.082; 95% CI, 0.059 to 0.106; $P < 0.0001$; TONADO 2, MD 0.088; 95% CI, 0.063 to 0.113; $P < 0.0001$) (Table 31). Similar differences between the TIO/OLO 5/5 mcg group and the TIO 5 mcg and OLO 5 mcg groups were seen in mean trough FEV_1 response after 52 weeks of treatment (Table 42). In OTEMTO 1 and OTEMTO 2, there was a statistically significantly greater mean trough FEV_1 response at week 12 in the TIO/OLO 5/5 mcg group compared with the placebo group ($P < 0.0001$). There was a difference between the TIO/OLO 5/5 mcg group and the TIO 5 mcg group, which was statistically significant only in OTEMTO 2 (MD 0.039 L; 95% CI, 0.002 to 0.076; $P = 0.0395$; not in testing hierarchy). Trough FEV_1 response was not included in the statistical testing hierarchy in VIVACITO, the exercise endurance studies, and ENERGITO, but in general the TIO/OLO 5/5 mcg groups had a greater mean trough FEV_1 response than the TIO 5 mcg, OLO 5 mcg, and placebo groups at the end of treatment. In the case of ENERGITO, the TIO/OLO 5/5 mcg group had a greater mean trough FEV_1 response at week 6 than the FP/SAL 500/50 mcg and 250/50 mcg groups. The generally accepted MCID for differences between active drug and placebo is between 0.10 and 0.14 L for change in trough FEV_1; however, the MCID for the difference between two active comparators is uncertain.

b) Forced expiratory volume in one second area under the curve

A primary end point in the 52-week studies (TONADO 1 and TONADO 2) and the 12-week phase 3b studies (OTEMTO 1 and OTEMTO 2) was the FEV_1 $AUC_{0–3h}$ response (change from baseline FEV_1). In TONADO 1 and TONADO 2, the adjusted mean FEV_1 $AUC_{0–3h}$ response was statistically significantly greater in the TIO/OLO 5/5 mcg group than the TIO 5 mcg group (TONADO 1, MD 0.117 L; 95% CI, 0.094 to 0.140; $P < 0.0001$; TONADO 2, MD 0.103 L; 95% CI, 0.078 to 0.127; $P < 0.0001$) and OLO 5 mcg group (TONADO 1, MD 0.123 L; 95% CI, 0.100 to 0.146; $P < 0.0001$; TONADO 2, MD 0.132 L; 95% CI, 0.108 to 0.157; $P < 0.0001$) (Table 31). Similar results were seen at week 52 (Table 42). In OTEMTO 1 and OTEMTO 2, the FEV_1 $AUC_{0–3h}$ response was statistically significantly greater in the TIO/OLO 5/5 mcg group than the TIO 5 mcg group and the placebo group, but only the comparison against placebo was included in the statistical testing hierarchy.

The FEV_1 $AUC_{0–24h}$ response, FEV_1 $AUC_{0–12h}$ response, and FEV_1 $AUC_{12–24h}$ response at end of treatment were measured in VIVACITO and ENERGITO. In VIVACITO, the adjusted mean FEV_1 $AUC_{0–24h}$ response at week 6 (primary end point) was statistically significantly greater in the TIO/OLO 5/5 mcg group

compared with the TIO 5 mcg group (MD 0.110 L; 95% CI, 0.082 to 0.139; *P* < 0.0001), the OLO 5 mcg group (MD 0.115 L; 95% CI, 0.087 to 0.143; *P* < 0.0001), and the placebo group (MD 0.280 L; 95% CI, 0.252 to 0.309; *P* < 0.0001) (Table 33). In VIVACITO, similar results were seen for the FEV_1 $AUC_{0–12h}$ and FEV_1 $AUC_{12–24h}$ responses at week 6. In ENERGITO, the adjusted mean FEV_1 $AUC_{0–24h}$ response at week 6 (key secondary end point) was statistically significantly greater in the TIO/OLO 5/5 mcg group compared with FP/SAL 500/50 mcg group (MD 0.086 L; 95% CI, 0.065 to 0.107; *P* < 0.0001) and the FP/SAL 250/50 mcg group (MD 0.082 L; 95% CI, 0.061 to 0.103; *P* < 0.0001) (Table 36). In ENERGITO, similar results were seen for the FEV_1 $AUC_{0–12h}$ (primary end point) and FEV_1 $AUC_{12–24h}$ responses (not included in statistical testing hierarchy) at week 6 (Table 36).

3.6.5 Symptoms (including dyspnea)

The mean TDI focal score at week 24 was measured in TONADO 1 and TONADO 2 as an additional end point in the individual trials and as a secondary end point in a pre-specified pooled analysis of both trials. The mean TDI focal score at week 12 was measured as a secondary end point in OTEMTO 1 and OTEMTO 2. The MCID for TDI focal score is 1 point (see APPENDIX 4: VALIDITY OF OUTCOME MEASURES). In TONADO 1, there was a statistically significantly greater mean TDI focal score at week 24 in the TIO/OLO 5/5 mcg group compared with the TIO 5 mcg group (MD 0.497 units; 95% CI, 0.133 to 0.861; *P* = 0.0074) and OLO 5 mcg group (MD 0.721 units; 95% CI, 0.357 to 1.086; *P* = 0.0001). In TONADO 2, there was no difference seen in mean TDI focal score at week 24 between TIO/OLO 5/5 mcg and the individual components. In a pooled analysis of TONADO 1 and TONADO 2, there was a statistically significantly greater mean TDI focal score at week 24 in the TIO/OLO 5/5 mcg group compared with the TIO 5 mcg group (MD 0.356 units; 95% CI, 0.092 to 0.619) and OLO 5 mcg group (MD 0.420 units; 95% CI, 0.155 to 0.684) (Table 43). Although this pooled analysis was included in a statistical testing hierarchy (for European regulatory purposes), it fell below a statistically non-significant parameter in the chain. In OTEMTO 1 and OTEMTO 2, there was a statistically significantly greater mean TDI focal score at week 12 in the TIO/OLO 5/5 mcg group compared with the TIO 5 mcg group and the placebo group (Table 32), though this end point was not in the statistical testing hierarchy.

A TDI focal score responder was defined as a patient with a score ≥ 1 unit at week 24 in TONADO 1 and TONADO 2 and at week 12 in OTEMTO 1 and OTEMTO 2. Patients with missing TDI focal scores were considered non-responders. In TONADO 1, there was a greater proportion of responders in the TIO/OLO 5/5 mcg group (57.2%) compared with the TIO 5 mcg group (50.0%) and the OLO 5 mcg group (44.9%). In TONADO 2, there was no difference between groups in the proportion of responders. In OTEMTO 1 and OTEMTO 2, there was a greater proportion of responders in the TIO/OLO 5/5 mcg group (OTEMTO 1, %; OTEMTO 2, 51.3%) compared with the TIO 5 mcg group (OTEMTO 1, 47.7%; OTEMTO 2, 34.4%) and placebo group (OTEMTO 1, 23.5%; OTEMTO 2, 29.0%).

3.6.6 Health-related quality of life

The St. George's Respiratory Questionnaire (SGRQ) was used to assess quality of life in TONADO 1, TONADO 2, OTEMTO 1, and OTEMTO 2. Higher scores are indicative of greater impairment, and a change from baseline of 4 units is considered a clinically meaningful change (APPENDIX 4: VALIDITY OF OUTCOME MEASURES). In TONADO 1, SGRQ total score at week 24 was lower in the TIO/OLO 5/5 mcg group compared with the TIO 5 mcg group (MD −1.800; 95% CI, −3.305 to −0.294; *P* = 0.0192) and the OLO 5 mcg group (MD −2.583; 95% CI, −4.103 to −1.063; *P* = 0.0009) (Table 31). Similar results were seen in TONADO 1 at week 52 (Table 42). In TONADO 2, there was no difference in SGRQ total score at week 24 between the TIO/OLO 5/5 mcg group and the other treatment groups (Table 31). For the individual trials, this end point was not included in the statistical testing hierarchy. In a pre-specified pooled analysis of TONADO 1 and TONADO 2, SGRQ total score at week 24 was the primary end point. In

this pooled analysis, there was a statistically significantly lower SGRQ total score at week 24 in the TIO/OLO 5/5 mcg group compared with the TIO 5 mcg group MD −1.233; 95% CI, −2.313 to −0.153; *P* = 0.0252) and the OLO 5 mcg group (MD −1.693; 95% CI, −2.778 to −0.608; *P* = 0.0022) (Table 43). In OTEMTO 1 and OTEMTO 2, SGRQ total score at week 12 was lower in the TIO/OLO 5/5 mcg group compared with the placebo group (OTEMTO 1, MD −4.894; 95% CI, −6.904 to −2.884; *P* < 0.0001; OTEMTO 2, MD −4.564; 95% CI, −6.499 to −2.629; *P* < 0.0001) (Table 32).

An SGRQ total score responder was defined as a patient with an improvement in total score of ≥ 4 units from baseline at week 24 in TONADO 1 and TONADO 2, and at week 12 in OTEMTO 1 and OTEMTO 2. Patients with missing SGRQ total scores were considered non-responders. In TONADO 1 and TONADO 2, there was a greater proportion of responders in the TIO/OLO 5/5 mcg group (TONADO 1, 59.2%; TONADO 2, 55.9%) compared with the TIO 5 mcg group (TONADO 1, 48.3%; TONADO 2, 49.1%) and the OLO 5 mcg group (TONADO 1, 43.3%; TONADO 2, 46.3%). In OTEMTO 1 and OTEMTO 2, there was a greater proportion of responders in the TIO/OLO 5/5 mcg group (OTEMTO 1, 53.1%; OTEMTO 2, 51.8%) compared with the TIO 5 mcg group (OTEMTO 1, 41.7%; OTEMTO 2, 41.1%) and placebo group (OTEMTO 1, 31.2%; OTEMTO 2, 32.6%).

3.6.7 Exercise tolerance

a) Exercise endurance time during constant work rate cycle ergometry, two hours post-dose

EET during CWRCE to symptom limitation at 75% maximal work capacity at the end of the treatment period was a primary end point in the exercise tolerance studies (MORACTO 1, MORACTO 2, and TORRACTO). CWRCE was started two hours after inhalation of study medication. In MORACTO 1 and MORACTO 2, there was a statistically significant increase in adjusted geometric mean endurance time during CWRCE after six weeks for TIO/OLO 5/5 mcg compared with placebo (MORACTO 1, 20.9% increase; *P* < 0.0001; MORACTO 2, 13.4% increase; *P* < 0.0001) (Table 34). In MORACTO 2, there was also a statistically significant increase in adjusted mean endurance time during CWRCE after six weeks for TIO/OLO 5/5 mcg compared with OLO 5 mcg (11.1% increase; *P* = 0.0009). There was no increase in endurance time for TIO/OLO 5/5 mcg compared with TIO 5 mcg and OLO 5 mcg in MORACTO 1 and compared with TIO 5 mcg in MORACTO 2. In TORRACTO, there was a statistically significant increase in endurance time during CWRCE after 12 weeks compared with placebo (13.8% increase; *P* = 0.0209) (Table 35).

b) Exercise endurance time during endurance shuttle walk test, two hours post-dose

The ESWT was performed in a subset of patients in TORRACTO, and the EET during ESWT to symptom limitation at a walking speed corresponding to 85% of predicted peak oxygen consumption after 12 weeks was a key secondary end point. ESWT was started two hours after inhalation of study medication. All statistical tests for the ESWT are considered descriptive because they fell below a statistically non-significant parameter in the testing hierarchy. After 12 weeks of treatment, the adjusted geometric mean endurance time increased by 20.9% for TIO/OLO 5/5 mcg compared with placebo (*P* = 0.0552) (Table 35).

c) Inspiratory capacity at rest before constant work rate cycle ergometry

Inspiratory capacity at rest before CWRCE was assessed as a primary end point in MORACTO 1 and MORACTO 2 and as a secondary end point in TORRACTO. In MORACTO 1 and MORACTO 2 there was a statistically significantly greater increase in inspiratory capacity at rest at week 6 for TIO/OLO 5/5 mcg compared with the monotherapy components and placebo (*P* < 0.0001 to *P* = 0.0015; Table 34). In TORRACTO, there was a statistically significantly greater increase in inspiratory capacity at rest at

week 12 for TIO/OLO 5/5 mcg compared with placebo, but differences were considered descriptive because this testing fell below a non-significant parameter in the testing hierarchy (Table 35).

d) Breathing discomfort (dyspnea)

Dyspnea during exercise was measured in the exercise endurance studies using the modified Borg scale, where higher scores are indicative of more severe dyspnea. The slope of the intensity of breathing discomfort relative to exercise time during CWRCE was calculated as a secondary end point in MORACTO 1, MORACTO 2, and TORRACTO. A decrease in the slope of the intensity of breathing discomfort during exercise reflects a treatment benefit. All statistical analyses for this end point are considered descriptive as they were not included in the statistical testing hierarchy. The adjusted mean slope of the intensity of breathing discomfort was reduced for TIO/OLO 5/5 mcg compared with placebo after 6 weeks in MORACTO 1 and MORACTO 2 (MD −0.003 Borg units/second; $P < 0.0001$), and after 12 weeks in TORRACTO (MD −0.003 Borg units/second; $P = 0.0598$) (Table 34 and Table 35). A change of one unit is considered a clinically meaningful change in the modified Borg scale (APPENDIX 4: VALIDITY OF OUTCOME MEASURES).

TABLE 31: KEY EFFICACY OUTCOMES — 52-WEEK PARALLEL-GROUP STUDIES (TONADO 1, TONADO 2)

Outcome	TONADO 1 (1237.5)			TONADO 2 (1237.6)		
	TIO/OLO 5/5 mcg (N = 522)	TIO 5 mcg (N = 527)	OLO 5 mcg (N = 528)	TIO/OLO 5/5 mcg (N = 507)	TIO 5 mcg (N = 506)	OLO 5 mcg (N = 510)
Deaths, n (%)						
All-cause	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CV-related[f]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COPD-related[f]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COPD exacerbations, n (%)						
Any exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Annual rate/PY (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rate ratio (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Requiring hospitalization	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Annual rate/PY (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rate ratio (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to first COPD exacerbation, day	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI), TIO/OLO vs. comparator	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Outcome	TONADO 1 (1237.5)			TONADO 2 (1237.6)		
	TIO/OLO 5/5 mcg (N = 522)	TIO 5 mcg (N = 527)	OLO 5 mcg (N = 528)	TIO/OLO 5/5 mcg (N = 507)	TIO 5 mcg (N = 506)	OLO 5 mcg (N = 510)
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FEV_1 $AUC_{0–3h}$ response (L), week 24, co-*primary end point*						
N[a]	522	526	525	502	500	507
Common baseline mean (SE)[a]	[redacted]			[redacted]		
Adjusted mean response (SE)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	0.117 (0.094 to 0.140)	0.123 (0.100 to 0.146)	-	0.103 (0.078 to 0.127)	0.132 (0.108 to 0.157)
P value	-	< 0.0001	< 0.0001	-	< 0.0001	< 0.0001
Trough FEV_1 response (L), week 24, *co-primary end point*						
N[a]	521	520	519	497	498	503
Common baseline mean (SE)[a]	[redacted]			[redacted]		
Adjusted mean response (SE)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	0.071 (0.047 to 0.094)	0.082 (0.059 to 0.106)	-	0.050 (0.024 to 0.075)	0.088 (0.063 to 0.113)
P value	-	< 0.0001	< 0.0001	-	0.0001	< 0.0001
TDI focal score, week 24						
N	509	498	503	484	480	481
Common baseline mean (SE)[a]	[redacted]			[redacted]		
Adjusted mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted MD (95% CI), TIO/OLO vs. comparator	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responder, n (%)[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SGRQ total score, week 24						
N	502	487	483	478	468	471
Common baseline mean (SE)[a]	[redacted]			[redacted]		

Outcome	TONADO 1 (1237.5)			TONADO 2 (1237.6)		
	TIO/OLO 5/5 mcg (N = 522)	TIO 5 mcg (N = 527)	OLO 5 mcg (N = 528)	TIO/OLO 5/5 mcg (N = 507)	TIO 5 mcg (N = 506)	OLO 5 mcg (N = 510)
Adjusted mean (SE)	[redacted]					
Adjusted MD (95% CI), TIO/OLO vs. comparator		[redacted]				
P value		[redacted]				
Responder, n (%)[e]	[redacted]					
Use of daytime rescue medication at week 52, number of puffs per day						
N	[redacted]					
Common baseline mean (SE)[a]	[redacted]					
Adjusted mean (SE)	[redacted]					
Adjusted MD (95% CI), TIO/OLO vs. comparator		[redacted]				
P value		[redacted]				
Use of nighttime rescue medication at week 52, number of puffs per day						
N	[redacted]					
Common baseline mean (SE)[a]	[redacted]					
Adjusted mean (SE)	[redacted]					
Adjusted MD (SE), TIO/OLO vs. comparator		[redacted]				
P value		[redacted]				

AUC = area under the curve; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; FEV_1 = forced expiratory volume in 1 second; HR = hazard ratio; MD = mean difference; MMRM = mixed model for repeated measures; OLO = olodaterol; PY = patient-year; SE = standard error; SGRQ = St. George's Respiratory Questionnaire; TDI = transition dyspnea index; TIO = tiotropium; vs. = versus.

[a] Number of patients contributing to MMRM; baseline mean calculated from all patients contributing to MMRM.

[b] MMRM including treatment, planned test day, treatment-by-test-day interaction, baseline, and baseline-by-test day interaction as fixed effects, and patient as random effect.

[c] No control for statistical testing outside the testing hierarchy.

[d] Defined as TDI focal score ≥ 1.

[e] Defined as an improvement of SGRQ total score ≥ 4.0 from baseline.

[f] As assessed by the mortality adjudication committee.

Source: Clinical Study Reports.[1,2]

TABLE 32: KEY EFFICACY OUTCOMES — 12-WEEK PHASE 3B STUDIES (OTEMTO 1, OTEMTO 2)

Outcome	OTEMTO 1 (1237.25)			OTEMTO 2 (1237.26)		
	TIO/OLO 5/5 mcg (N = 203)	TIO 5 mcg (N = 203)	Placebo (N = 204)	TIO/OLO 5/5 mcg (N = 202)	TIO 5 mcg (N = 203)	Placebo (N = 202)
Deaths, n (%)						
All-cause	[redacted]					
CV-related						
COPD-related						
COPD exacerbations, n (%)						
Any exacerbation	[redacted]					
Requiring hospitalization						
FEV_1 $AUC_{0–3h}$ response (L), week 12, co-*primary end point*						
N[a]	202	203	204	200	201	199
Common baseline mean (SE)[a]	1.296 (0.018)			1.323 (0.017)		
Adjusted mean response (SE)[b]	[redacted]					
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	0.111 (0.075 to 0.148)	0.331 (0.293 to 0.369)	-	0.105 (0.069 to 0.141)	0.299 (0.261 to 0.336)
P value	-	< 0.0001[c]	< 0.0001	-	< 0.0001[c]	< 0.0001
Trough FEV_1 response (L), week 12, *co-primary end point*						
N[a]	200	200	198	199	197	193
Common baseline mean (SE)[a]	1.298 (0.018)			1.329 (0.017)		
Adjusted mean response (SE)[b]	[redacted]					
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	0.028 (−0.009 to 0.066)	0.162 (0.124 to 0.200)	-	0.039 (0.002 to 0.076)	0.166 (0.129 to 0.203)
P value	-	0.1381[c]	< 0.0001	-	0.0395[c]	< 0.0001
TDI focal score, week 12, *secondary end point*						
N	196	193	187	197	192	183
Common baseline mean (SE)[a]	6.421 (0.073)			6.653 (0.075)		
Adjusted mean (SE)	1.939 (0.190)	1.332 (0.192)	−0.113 (0.196)	1.531 (0.187)	0.950 (0.191)	0.337 (0.195)
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	0.607 (0.078 to 1.137)	2.052 (1.516 to 2.588)	-	0.582 (0.058, 1.106)	1.195 (0.665 to 1.725)
P value	-	0.0246[c]	< 0.0001[c]	-	0.0296[c]	< 0.0001[c]
Responder, n (%)[d]	[redacted]					

Outcome	OTEMTO 1 (1237.25)			OTEMTO 2 (1237.26)		
	TIO/OLO 5/5 mcg (N = 203)	TIO 5 mcg (N = 203)	Placebo (N = 204)	TIO/OLO 5/5 mcg (N = 202)	TIO 5 mcg (N = 203)	Placebo (N = 202)
SGRQ total score, week 12, *co-primary end point*						
N	196	192	186	197	192	184
Common baseline mean (SE)[a]	42.433 (0.622)			42.700 (0.617)		
Adjusted mean (SE)	37.144 (0.710)	39.637 (0.717)	42.038 (0.738)	38.011 (0.683)	39.729 (0.694)	45.575 (0.711)
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	−2.493 (−4.473 to −0.513)	−4.894 (−6.904 to −2.884)	-	−1.717 (−3.628 to 0.193)	−4.564 (−6.499 to −2.629)
P value	-	0.0136[c]	< 0.0001	-	0.0780[c]	< 0.0001
Responder, n (%)[e]	104 (53.1)	80 (41.7)	58 (31.2)	102 (51.8)	79 (41.1)	60 (32.6)
Use of daytime rescue medication at week 12, number of puffs per day						
N	[redacted]					
Common baseline mean (SE)[a]	[redacted]					
Adjusted mean (SE)	[redacted]					
Adjusted MD (95% CI), TIO/OLO vs. comparator	[redacted]					
P value	[redacted]					
Use of nighttime rescue medication at week 12, number of puffs per day						
N	[redacted]					
Common baseline mean (SE)[a]	[redacted]					
Adjusted mean (SE)	[redacted]					
Adjusted MD (SE), TIO/OLO vs. comparator	[redacted]					
P value	[redacted]					

AUC = area under the curve; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; FEV_1 = forced expiratory volume in 1 second; MD = mean difference; MMRM = mixed model for repeated measures; OLO = olodaterol; SE = standard error; SGRQ = St. George's Respiratory Questionnaire; TDI = transition dyspnea index; TIO = tiotropium; vs. = versus.

[a] Number of patients contributing to MMRM; baseline mean calculated from all patients contributing to MMRM.

[b] MMRM including treatment, planned test day, treatment-by-test-day interaction, baseline, and baseline-by-test-day interaction as fixed effects, and patient as random effect.

[c] No control for statistical testing outside the testing hierarchy.

[d] Defined as TDI focal score ≥ 1.

[e] Defined as an improvement of SGRQ total score ≥ 4.0 from baseline.

Source: Clinical Study Reports.[3,4]

TABLE 33: KEY EFFICACY OUTCOMES — SIX-WEEK LUNG FUNCTION PROFILE CROSSOVER STUDY (VIVACITO)

Outcome	VIVACITO (1237.20)			
	TIO/OLO 5/5 mcg (n = 139)	TIO 5 mcg (n = 138)	OLO 5 mcg (n = 138)	Placebo (n = 138)
Deaths, n (%)				
All-cause	0	0	0	0
COPD exacerbations, n (%)				
Any exacerbation	[redacted]	[redacted]	[redacted]	[redacted]
Requiring hospitalization	[redacted]	[redacted]	[redacted]	[redacted]
FEV_1 $AUC_{0–24h}$ response (L), week 6, *primary end point*				
N[a]	138	135	136	132
Common baseline mean (SE)[a]	1.301 (0.030)			
Adjusted mean response (SE)[b]	0.244 (0.013)	0.133 (0.014)	0.129 (0.013)	−0.037 (0.014)
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	0.110 (0.082 to 0.139)	0.115 (0.087 to 0.143)	0.280 (0.252 to 0.309)
P value	-	< 0.0001	< 0.0001	< 0.0001
FEV_1 $AUC_{0–12h}$ response (L), week 6, *secondary end point*				
N[a]	138	135	136	132
Common baseline mean (SE)[a]	1.301 (0.030)			
Adjusted mean response (SE)[b]	0.305 (0.015)	0.186 (0.015)	0.179 (0.015)	−0.013 (0.015)
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	0.119 (0.089 to 0.149)	0.126 (0.096 to 0.156)	0.319 (0.289 to 0.349)
P value	-	< 0.0001	< 0.0001	< 0.0001
FEV_1 $AUC_{12–24h}$ response (L), week 6, *secondary end point*				
N[a]	138	135	136	132
Common baseline mean (SE)[a]	1.301 (0.030)			
Adjusted mean response (SE)[b]	0.182 (0.013)	0.081 (0.014)	0.079 (0.013)	−0.060 (0.014)
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	0.102 (0.072 to 0.132)	0.103 (0.074 to 0.133)	0.243 (0.212 to 0.273)
P value	-	< 0.0001	< 0.0001	< 0.0001
FEV_1 $AUC_{0–3h}$ response (L), week 6, *additional end point*				
N[a]	138	137	138	135
Common baseline mean (SE)[a]	1.301 (0.030)			
Adjusted mean response (SE)[b]	0.332 (0.015)	0.223 (0.016)	0.223 (0.015)	0.007 (0.016)

Outcome	VIVACITO (1237.20)			
	TIO/OLO 5/5 mcg (n = 139)	TIO 5 mcg (n = 138)	OLO 5 mcg (n = 138)	Placebo (n = 138)
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	0.109 (0.077, 0.141)	0.109 (0.078, 0.141)	0.325 (0.293, 0.357)
P value	-	< 0.0001[c]	< 0.0001[c]	< 0.0001[c]
Trough FEV_1 response (L), week 6, *additional end point*				
N[a]	138	135	136	132
Common baseline mean (SE)[a]	1.301 (0.030)			
Adjusted mean response (SE)[b]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	0.079 (0.045 to 0.113)	0.092 (0.059 to 0.126)	0.207 (0.173 to 0.241)
P value	[redacted]	[redacted]	[redacted]	[redacted]

AUC = area under the curve; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; FEV_1 = forced expiratory volume in 1 second; MD = mean difference; MMRM = mixed model for repeated measures; OLO = olodaterol; SE = standard error; TIO = tiotropium; vs. = versus.

[a] Number of patients with measurements available at week 6; baseline mean calculated from all patients with measurements available at week 6.

[b] MMRM with treatment and period as fixed effects, patient baseline and period baseline as covariates, and patient as random effect.

[c] No control for statistical testing outside the testing hierarchy.

Source: Clinical Study Report.[5]

TABLE 34: KEY EFFICACY OUTCOMES — SIX-WEEK CROSSOVER EXERCISE TOLERANCE STUDIES (MORACTO 1, MORACTO 2)

Outcome	MORACTO 1 (1237.13)				MORACTO 2 (1237.14)			
	TIO/OLO 5/5 mcg	TIO 5 mcg	OLO 5 mcg	Placebo	TIO/OLO 5/5 mcg	TIO 5 mcg	OLO 5 mcg	Placebo
N	226	226	217	222	224	218	218	214
Deaths, n (%)								
All-cause	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CV-related	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COPD exacerbations, n (%)								
Any exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Requiring hospitalization	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FEV_1 one hour post-dose (L), week 6, *secondary end point*								
N[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Common baseline mean (SE)[a]	[redacted]				[redacted]			

Outcome	MORACTO 1 (1237.13)				MORACTO 2 (1237.14)			
	TIO/OLO 5/5 mcg	TIO 5 mcg	OLO 5 mcg	Placebo	TIO/OLO 5/5 mcg	TIO 5 mcg	OLO 5 mcg	Placebo
Adjusted mean (SE)[b]	[redacted]							
Adjusted MD (95% CI), TIO/OLO vs. comparator	[redacted]							
P value	[redacted]							
Trough FEV_1 response (L), week 6, *additional end point*								
N[a]	[redacted]							
Common baseline mean (SE)[a]	[redacted]							
Adjusted mean (SE)[b]	[redacted]							
Adjusted MD (95% CI), TIO/OLO vs. comparator	[redacted]							
P value	[redacted]							
IC at rest (L), week 6, *co-primary end point*								
N[a]	219	213	214	211	218	208	208	202
Common baseline mean (SE)[a]	2.533 (0.042)				2.589 (0.044)			
Adjusted mean (SE)[b]	2.685 (0.027)	2.571 (0.027)	2.566 (0.027)	2.440 (0.027)	2.767 (0.025)	2.679 (0.025)	2.687 (0.025)	2.502 (0.026)
Adjusted MD (95% CI), TIO/OLO vs. comparator	[redacted]							
P value	[redacted]							
EET during CWRCE at 75% Wcap (seconds), week 6, *co-primary end point*								
N[a]	212	209	208	209	216	209	207	205
Common baseline mean (SE)[a]	459.95 (13.941)				434.31 (14.163)			
Adjusted mean (SE)[b,d]	454.08 (14.474)	457.16 (14.652)	453.38 (14.552)	375.45 (12.037)	465.68 (13.359)	446.50 (12.958)	419.06 (12.207)	410.77 (12.009)
Adjusted mean ratio (95% CI), TIO/OLO vs. comparator[d]	[redacted]							
P value	-	0.8415	0.9633	< 0.0001	-	0.1807	0.0009	< 0.0001
Slope of intensity of breathing discomfort during CWRCE (units/second),[e] week 6, *secondary end point*								
N[a]	[redacted]							

Outcome	MORACTO 1 (1237.13)				MORACTO 2 (1237.14)			
	TIO/OLO 5/5 mcg	TIO 5 mcg	OLO 5 mcg	Placebo	TIO/OLO 5/5 mcg	TIO 5 mcg	OLO 5 mcg	Placebo
Common baseline mean slope (SE)[a]								
Adjusted mean (SE)[b]								
Adjusted MD (95% CI), TIO/OLO vs. comparator								
P value								

CI = confidence interval; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; CWRCE = constant work rate cycle ergometry; EET = exercise endurance time; FEV_1 = forced expiratory volume in 1 second; IC = inspiratory capacity; MD = mean difference; MMRM = mixed model for repeated measures; OLO = olodaterol; SE = standard error; TIO = tiotropium; vs. = versus; Wcap = maximal work capacity.

[a] Number of patients contributing to the MMRM model; baseline mean calculated from all patients contributing to MMRM.

[b] MMRM with treatment and period as fixed effects, study baseline as covariate, patient as random effect, and compound symmetry as a covariance structure for within-patient variation.

[c] No control for statistical testing, outside of the testing hierarchy.

[d] Mean and confidence intervals were transformed from $\log_{10}$ back to the original scale.

[e] Defined as (Borg scale of breathing discomfort at the end of exercise minus Borg scale of breathing discomfort at pre-exercise)/endurance time.

Source: Clinical Study Reports.[6,7]

TABLE 35: KEY EFFICACY OUTCOMES — 12-WEEK PARALLEL-GROUP EXERCISE TOLERANCE STUDY (TORRACTO)

Outcome	TORRACTO (1237.15)	
	TIO/ OLO 5/5 mcg (n = 139)	Placebo (n = 132)
Deaths, n (%)		
All-cause	[redacted]	[redacted]
COPD exacerbations, n (%)		
Any exacerbation	[redacted]	[redacted]
Requiring hospitalization	[redacted]	[redacted]
FEV_1 one hour post-dose (L), week 12, *secondary end point*		
N[a]	[redacted]	[redacted]
Common baseline mean (SE)[a]	[redacted]	
Adjusted mean (SE)[b]	[redacted]	[redacted]
Adjusted MD (95% CI), TIO/OLO vs. comparator	[redacted]	[redacted]
P value	[redacted]	[redacted]
Trough FEV_1 response (L), week 12, *additional end point*		
N[a]	[redacted]	[redacted]
Common baseline mean (SE)[a]	[redacted]	
Adjusted mean (SE)[b]	[redacted]	[redacted]
Adjusted MD (95% CI), TIO/OLO vs. comparator	[redacted]	[redacted]
P value	[redacted]	[redacted]
IC at rest before CWRCE (L), week 12, *secondary end point*		
N[a]	[redacted]	[redacted]
Common baseline mean (SE)[a]	[redacted]	
Adjusted mean (SE)[b]	[redacted]	[redacted]
Adjusted MD (95% CI), TIO/OLO vs. comparator	[redacted]	[redacted]
P value	[redacted]	[redacted]
EET during CWRCE at 75% Wcap (seconds), week 12, *primary end point*		
N[a]	135	121
Common baseline mean (SE)[a]	443.0 (12.38)	
Adjusted mean (SE)[b,d]	527.51 (20.154)	463.63 (18.813)
Adjusted mean ratio (95% CI), TIO/OLO vs. comparator[d]	-	1.138 (1.020 to 1.269)
P value	-	0.0209
EET during ESWT at 85% VO_2 peak (seconds)[f], week 12, *secondary end point*		
N[a]	59	50
Common baseline mean (SE)[a]	311.2 (13.68)	
Adjusted mean (SE)[b,d]	376.39 (25.033)	311.41 (22.519)
Adjusted mean ratio (95% CI), TIO/OLO vs. comparator[d]	-	1.209 (0.996 to 1.467)
P value	-	0.0552[g]

Outcome	TORRACTO (1237.15)	
	TIO/ OLO 5/5 mcg (n = 139)	Placebo (n = 132)
Slope of intensity of breathing discomfort during CWRCE (units/second),[e] week 12, *secondary end point*		
N[a]	[redacted]	[redacted]
Common baseline mean slope (SE)[a]	[redacted]	
Adjusted mean (SE)[b]	[redacted]	[redacted]
Adjusted MD (95% CI), TIO/OLO vs. comparator	[redacted]	[redacted]
P value	[redacted]	[redacted]

CI = confidence interval; CV = cardiovascular; COPD = chronic obstructive pulmonary disease; CWRCE = constant work rate cycle ergometry; EET = exercise endurance time; ESWT = endurance shuttle walk test; FEV_1 = forced expiratory volume in 1 second; IC = inspiratory capacity; MD = mean difference; MMRM = mixed model for repeated measures; OLO = olodaterol; SE = standard error; TIO = tiotropium; VO_2 peak = maximal oxygen consumption; vs. = versus; Wcap = maximal work capacity.
[a] Number of patients contributing to the MMRM model; baseline mean calculated from all patients contributing to MMRM.
[b] MMRM including treatment, planned test day, treatment-by-test-day interaction, baseline, and baseline-by-test day interaction as fixed effects, patient as random effect, and compound symmetry as covariance structure for within-patient variation.
[c] No control for statistical testing, outside of the testing hierarchy.
[d] Mean and confidence intervals were transformed from log_{10} back to the original scale.
[e] Defined as (Borg scale of breathing discomfort at the end of exercise minus Borg scale of breathing discomfort at pre-exercise)/endurance time.
[f] Conducted at select centres.
[g] Descriptive as outcome fell below a statistically non-significant parameter in the testing hierarchy.
Source: Clinical Study Report.[8]

TABLE 36: KEY EFFICACY OUTCOMES — SIX-WEEK TIOTROPIUM/OLODATEROL VERSUS FLUTICASONE PROPIONATE/SALMETEROL CROSSOVER STUDY (ENERGITO)

Outcome	ENERGITO (1237.11)		
	TIO/OLO 5/5 mcg (n = 221)	FP/SAL 500/50 mcg (n = 219)	FP/SAL 250/50 mcg (n = 212)
Deaths, n (%)			
All-cause	2 (0.9)	0	0
CV-related	1 (0.5)	0	0
COPD exacerbations, n (%)			
Any exacerbation	[redacted]	[redacted]	[redacted]
Requiring hospitalization	[redacted]	[redacted]	[redacted]
FEV_1 $AUC_{0–12h}$ response (L), week 6, *primary end point*			
N[a]	[redacted]	[redacted]	[redacted]
Common baseline mean (SE)[a]	[redacted]		
Adjusted mean (SE)[b]	[redacted]	[redacted]	[redacted]
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	0.129 (0.107 to 0.150)	0.125 (0.103 to 0.147)
P value	-	< 0.0001	< 0.0001
FEV_1 $AUC_{0–24h}$ response (L), week 6, *key secondary end point*			
N[a]	[redacted]	[redacted]	[redacted]

Outcome	ENERGITO (1237.11)		
	TIO/OLO 5/5 mcg (n = 221)	FP/SAL 500/50 mcg (n = 219)	FP/SAL 250/50 mcg (n = 212)
Common baseline mean (SE)[a]	[redacted]		
Adjusted mean (SE)[b]	[redacted]	[redacted]	[redacted]
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	0.086 (0.065 to 0.107)	0.082 (0.061 to 0.103)
P value	-	< 0.0001	< 0.0001
FEV_1 $AUC_{12–24h}$ response (L), week 6, *other secondary end point*			
N[a]	[redacted]	[redacted]	[redacted]
Common baseline mean (SE)[a]	[redacted]		
Adjusted mean (SE)[b]	[redacted]	[redacted]	[redacted]
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	0.043 (0.021 to 0.065)	0.039 (0.017 to 0.062)
P value	-	0.0002[c]	0.0007[c]
Trough FEV_1 response (L), week 6, *other secondary end point*			
N[a]	[redacted]	[redacted]	[redacted]
Common baseline mean (SE)[a]	[redacted]		
Adjusted mean (SE)[b]	[redacted]	[redacted]	[redacted]
Adjusted MD (95% CI), TIO/OLO vs. comparator	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]

AUC = area under the curve; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; FEV_1 = forced expiratory volume in 1 second; FP = fluticasone propionate; MD = mean difference; MMRM = mixed model for repeated measures; OLO = olodaterol; SAL = salmeterol; SE = standard error; TIO = tiotropium, vs. = versus.
[a] Number of patients contributing to MMRM; baseline mean calculated from all patients contributing to MMRM.
[b] MMRM with treatment and period as fixed effects, patient as random effect, patient baseline and period baseline as covariates, and compound symmetry as a covariance structure for within-patient variation.
[c] No control for statistical testing outside the testing hierarchy.
Source: Clinical Study Report.[9]

3.6.8 Other efficacy outcomes

a) Use of rescue medication

The use of daytime and nighttime rescue medication was assessed throughout the treatment period in TONADO 1, TONADO 2, OTEMTO 1, and OTEMTO 2, and results for the last week of treatment are presented (Table 31 and Table 32). In TONADO 1 and TONADO 2, reductions in the weekly mean use of rescue medication during the daytime and nighttime were observed in all treatment groups compared with baseline. Statistical testing was considered exploratory as this end point was not included in the statistical testing hierarchy. At week 52, there was a greater decrease in the mean number of puffs per day of daytime rescue medication compared with baseline for the TIO/OLO 5/5 mcg group compared with the TIO group (TONADO 1, MD −0.262 puffs/day, *P* = 0.0018; TONADO 2, MD −0.261 puffs/day, *P* = 0.0042), and in the mean number of puffs per day of nighttime rescue medication compared with baseline (TONADO 1, MD −0.537 puffs/day, *P* < 0.0001; TONADO 2, MD −0.579 puffs/day, *P* < 0.0001). In OTEMTO 1 and OTEMTO 2, there was a greater decrease in the mean number of puffs per day of

daytime rescue medication at week 12 compared with baseline for the TIO/OLO 5/5 mcg group compared with the placebo group (Table 32).

b) Patient satisfaction

Patient satisfaction was not measured or reported in the included studies.

c) Days of missed work or school

No data for days of missed work or school were reported in the included studies.

3.7 Harms

Only those harms identified in the review protocol are reported here. See APPENDIX 3: DETAILED OUTCOME DATA for detailed harms data.

3.7.1 Adverse events

In the 52-week studies (TONADO 1 and TONADO 2), the proportion of patients experiencing an AE ranged from 72.3% to 79.4% across the treatment groups (Table 37). In the 12-week studies (OTEMTO 1, OTEMTO 2, and TORRACTO), the proportion of patients experiencing an AE ranged from 43.1% to 51.5%, with a slightly higher proportion of patients in the placebo groups compared with the other treatment groups (Table 38 and Table 40). In the six-week studies (VIVACITO, MORACTO 1, MORACTO 2, and ENERGITO), the proportion of patients experiencing an AE ranged from 29.7% in the FP/SAL 250/500 mcg group of ENERGITO to 46.4% in the placebo group of VIVACITO (Table 39, Table 40, and Table 41). The most common AEs across all trials were COPD exacerbations and nasopharyngitis.

3.7.2 Serious adverse events

In the 52-week studies (TONADO 1 and TONADO 2), the proportion of patients experiencing an SAE ranged from 14.2% to 20.8% across treatment groups (Table 37). In the six- and 12-week studies, the proportion of patients experiencing an SAE ranged from 0.7% to 5.9%. Generally, the proportion of patients experiencing an SAE across treatment groups within studies was not remarkable different.

3.7.3 Withdrawals due to adverse events

In the 52-week studies (TONADO 1 and TONADO 2), the proportion of patients who withdrew due to an AE ranged from 7.1% to 10.6% across treatment groups. In the six- and 12-week studies, the proportion of patients who withdrew due to an AE ranged from 0.5% to 6.1%. Generally, a higher proportion of patients in the placebo groups withdrew due to an AE compared with the other treatment groups.

3.7.4 Notable harms

The proportion of patients experiencing a cardiovascular-related event was low across all studies. In the 52-week studies (TONADO 1 and TONADO 2), the most common cardiovascular-related event was hypertension, and the proportion of patients experiencing hypertension ranged from 2.2% to 5.1% across treatment groups (Table 37). Anticholinergic effects were generally rare across treatment groups and studies, ranging from 0% to 2.2% of patients across all treatment groups and studies. Cases of pneumonia were similarly rare across study groups and trials, ranging from 0% to 4.2% of patients affected.

TABLE 37: HARMS — 52-WEEK PARALLEL-GROUP STUDIES

Outcome	TONADO 1 (1237.5)			TONADO 2 (1237.6)		
	TIO/OLO 5/5 mcg (N = 522)	TIO 5 mcg (N = 527)	OLO 5 mcg (N = 528)	TIO/OLO 5/5 mcg (N = 507)	TIO 5 mcg (N = 506)	OLO 5 mcg (N = 510)
AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COPD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
URTI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COPD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WDAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Notable harms, n (%)						
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiovascular						
Arrhythmia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute MI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anticholinergic						
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dysphagia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blurred vision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; OLO = olodaterol; SAE = serious adverse event; TIO = tiotropium; URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse event.
Note: All notable harms set forth in the protocol are bolded.
Source: Clinical Study Reports.[1,2]

TABLE 38: HARMS — 12-WEEK PHASE 3B STUDIES (OTEMTO 1, OTEMTO 2)

Outcome	OTEMTO 1 (1237.25)			OTEMTO 2 (1237.26)		
	TIO/OLO 5/5 mcg (N = 203)	TIO 5 mcg (N = 203)	Placebo (N = 204)	TIO/OLO 5/5 mcg (N = 202)	TIO 5 mcg (N = 203)	Placebo (N = 202)
AEs, n (%)	91 (44.8)	90 (44.3)	105 (51.5)	87 (43.1)	93 (45.8)	93 (46.0)
COPD	10 (4.9)	20 (9.9)	23 (11.3)	10 (5.0)	8 (3.9)	15 (7.4)
Nasopharyngitis	7 (3.4)	9 (4.4)	12 (5.9)	10 (5.0)	8 (3.9)	8 (4.0)
URTI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	3 (1.5)	2 (1.0)	3 (1.5)	2 (1.0)	2 (1.0)	2 (1.0)
Bronchitis	1 (0.5)	2 (1.0)	2 (1.0)	2 (1.0)	5 (2.5)	3 (1.5)
Cough	4 (2.0)	3 (1.5)	6 (2.9)	3 (1.5)	5 (2.5)	12 (5.9)
Dyspnea	5 (2.5)	4 (2.0)	10 (4.9)	2 (1.0)	4 (2.0)	14 (6.9)
Headache	2 (1.0)	5 (2.5)	3 (1.5)	0	0	1 (0.5)
SAEs, n (%)	10 (4.9)	6 (3.0)	11 (5.4)	6 (3.0)	12 (5.9)	4 (2.0)
COPD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WDAEs, n (%)	3 (1.5)	3 (1.5)	11[a] (5.4)	1 (0.5)	7 (3.4)	10 (5.0)
Notable harms, n (%)						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiovascular						
Arrhythmia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute MI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ischemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anticholinergic						
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blurred vision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; OLO = olodaterol; SAE = serious adverse event; TIO = tiotropium; URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse event.
[a] Two patients in the placebo group were recorded as discontinuing study medication due to an AE. The AEs started before the patients had taken their first dose of study medication (and ended after they had started study treatment).
[b] Acute respiratory failure.
Source: Clinical Study Reports.[3,4]

TABLE 39: HARMS — SIX-WEEK LUNG FUNCTION PROFILE CROSSOVER STUDY (VIVACITO)

Outcome	VIVACITO (1237.20)			
	TIO/OLO 5/5 mcg (n = 139)	TIO 5 mcg (n = 138)	OLO 5 mcg (n = 138)	Placebo (n = 138)
AEs, n (%)	52 (37.4)	61 (44.2)	52 (37.7)	64 (46.4)
COPD	10 (7.2)	12 (8.7)	7 (5.1)	17 (12.3)
Nasopharyngitis	9 (6.5)	12 (8.7)	12 (8.7)	14 (10.1)
URTI	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]

Outcome	VIVACITO (1237.20)			
	TIO/OLO 5/5 mcg (n = 139)	TIO 5 mcg (n = 138)	OLO 5 mcg (n = 138)	Placebo (n = 138)
Bronchitis	[redacted]	[redacted]	[redacted]	[redacted]
Cough	7 (5.0)	6 (4.3)	2 (1.4)	7 (5.1)
Diarrhea	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnea	2 (1.4)	3 (2.2)	4 (2.9)	9 (6.5)
Headache	4 (2.9)	6 (4.3)	6 (4.3)	5 (3.6)
SAEs, n (%)	1 (0.7)	3 (2.2)	8 (5.8)	4 (2.9)
COPD	[redacted]	[redacted]	[redacted]	[redacted]
WDAEs, n (%)	1 (0.7)	2 (1.4)	3 (2.2)	5 (3.6)
Notable harms, n (%)				
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]
Cardiovascular				
Arrhythmia	[redacted]	[redacted]	[redacted]	[redacted]
Ischemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Anticholinergic				
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; COPD = chronic obstructive pulmonary disease; OLO = olodaterol; SAE = serious adverse event; TIO = tiotropium; URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse event.
[a] Acute respiratory failure.
Source: Clinical Study Report.[5]

TABLE 40: HARMS — EXERCISE TOLERANCE STUDIES

	MORACTO 1 (1237.13)				MORACTO 2 (1237.14)				TORRACTO (1237.15)	
	TIO/ OLO 5/5 mcg	TIO 5 mcg	OLO 5 mcg	Placebo	TIO/ OLO 5/5 mcg	TIO 5 mcg	OLO 5 mcg	Placebo	TIO/ OLO 5/5 mcg	Placebo
N	226	226	217	222	224	218	218	214	139	132
AEs, n (%)	87 (38.5)	77 (34.1)	87 (40.1)	89 (40.1)	93 (41.5)	93 (42.7)	88 (40.4)	89 (41.6)	61 (43.9)	67 (50.8)
COPD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
URTI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	MORACTO 1 (1237.13)				MORACTO 2 (1237.14)				TORRACTO (1237.15)	
	TIO/ OLO 5/5 mcg	TIO 5 mcg	OLO 5 mcg	Placebo	TIO/ OLO 5/5 mcg	TIO 5 mcg	OLO 5 mcg	Placebo	TIO/ OLO 5/5 mcg	Placebo
Dyspnea										
Headache										
Influenza										
SAEs, n (%)										
COPD										
WDAEs, n (%)										
Notable harms, n (%)										
Cardiac disorders										
Cardiovascular										
Arrhythmia										
Hypertension										
Ischemia										
Cardiac failure										
Anticholinergic										
Dizziness										
Dry mouth										
Pyrexia										
Blurred vision										
Pneumonia										

AE = adverse event; COPD = chronic obstructive pulmonary disease; OLO = olodaterol; SAE = serious adverse event; TIO = tiotropium; URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse event.
[a] Visual impairment.
Source: Clinical Study Report.[6-8]

TABLE 41: HARMS— SIX-WEEK TIOTROPIUM/OLODATEROL VERSUS FLUTICASONE PROPIONATE/SALMETEROL CROSSOVER STUDY (ENERGITO)

	ENERGITO (1237.11)		
	TIO/OLO 5/5 mcg (n = 221)	FP/SAL 500/50 mcg (n = 219)	FP/SAL 250/50 mcg (n = 212)
AEs, n (%)	75 (33.9)	81 (37.0)	63 (29.7)
COPD	20 (9.0)	19 (8.7)	9 (4.2)
Nasopharyngitis	12 (5.4)	11 (5.0)	13 (6.1)
Back pain	4 (1.8)	2 (0.9)	4 (1.9)
Cough	7 (3.2)	5 (2.3)	4 (1.9)
Diarrhea			
Dyspnea	3 (1.4)	6 (2.7)	4 (1.9)

	ENERGITO (1237.11)		
	TIO/OLO 5/5 mcg (n = 221)	FP/SAL 500/50 mcg (n = 219)	FP/SAL 250/50 mcg (n = 212)
Headache	8 (3.6)	2 (0.9)	4 (1.9)
SAEs, n (%)	7 (3.2)	9 (4.1)	4 (1.9)
COPD	[redacted]	[redacted]	[redacted]
WDAEs, n (%)	6 (2.7)	3 (1.4)	2 (0.9)
Notable harms, n (%)			
Cardiac disorders	[redacted]	[redacted]	[redacted]
Cardiovascular			
Acute MI	[redacted]	[redacted]	[redacted]
Ischemia	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Anticholinergic			
Dizziness	[redacted]	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]	[redacted]
Dysphagia	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]

AE = adverse event; COPD = chronic obstructive pulmonary disease; FP = fluticasone propionate; MI = myocardial infarction; OLO = olodaterol; SAE = serious adverse event; SAL = salmeterol; TIO = tiotropium; WDAE = withdrawal due to adverse event.
Source: Clinical Study Report.[9]

4. DISCUSSION

4.1 Summary of Available Evidence

Ten manufacturer-sponsored, double-blind, phase 3, randomized controlled trials conducted in patients with moderate to severe COPD were included in this review. Two replicate 52-week, parallel-group studies (TONADO 1 and TONADO 2) assessed the efficacy and safety of TIO/OLO 5/5 mcg versus its individual monocomponents, TIO 5 and OLO 5 mcg, for the co-primary end points of trough FEV_1 and FEV_1 $AUC_{0–3h}$ at week 24. One Japanese 52-week, parallel-group study (Study 1237.22) assessed the safety of TIO/OLO 5/5 mcg versus OLO 5 mcg for Japanese regulatory purposes, but due to a number of limitations (i.e., lack of adequate power, lack of generalizability, and post-hoc determination of primary end point), the presentation of data from this study is limited to Section 3.1 and Section 3.2.1 of this report. Two replicate, phase 3b, 12-week, parallel-group studies (OTEMTO 1 and OTEMTO 2) assessed the efficacy and safety of TIO/OLO 5/5 mcg versus TIO 5 mcg and placebo for the primary end points of trough FEV_1, FEV_1 $AUC_{0–3h}$, and SGRQ total score at the end of treatment. One six-week, incomplete crossover study (VIVACITO) assessed the 24-hour lung function profile of TIO/OLO 5/5 mcg versus its individual monocomponents and placebo for the primary end point of FEV_1 $AUC_{0–24h}$ at the end of treatment. Two replicate, six-week, incomplete crossover studies (MORACTO 1 and MORACTO 2) were exercise endurance studies designed to assess TIO/OLO 5/5 mcg versus its individual monocomponents and placebo for the co-primary end points of inspiratory capacity at rest and EET during cycle ergometry at the end of treatment. One 12-week, parallel-group study (TORRACTO) was an exercise endurance study designed to assess TIO/OLO 5/5 mcg versus placebo for the primary end point of EET during cycle ergometry, and a sub-study looking at EET during the endurance shuttle walk test was also conducted. One six-week, incomplete crossover study (ENERGITO) assessed the efficacy and safety of TIO/OLO 5/5 mcg versus FP/SAL 250/50 mcg and FP/SAL 500/50 mcg for the primary end point of FEV_1 $AUC_{0–12h}$ at the end of treatment.

The main limitations of the included studies were the short durations (6 weeks and 12 weeks), which may not be sufficient to assess key clinical outcomes such as mortality, quality of life, or COPD exacerbations. Although TONADO 1 and TONADO 2 were 52 weeks in duration, the primary outcomes were assessed at 24 weeks. There was a higher rate of discontinuations in the 12-week trials that included a placebo group (OTEMTO 1, OTEMTO 2, and TORRACTO), which could have potentially disrupted the balance of patient characteristics from randomization. The three-week washout period employed for crossover studies was sufficient for TIO/OLO and the individual components, but may not have been sufficient to wash out FP/SAL in the ENERGITO study. There were no studies with head-to-head comparisons of TIO/OLO 5/5 mcg and other LAMA/LABA combination therapies.

4.2 Interpretation of Results

4.2.1 Efficacy

Mortality and health care resource utilization were considered key outcomes in this review, but were not adequately assessed in the included studies. The six- and 12-week studies were too short in duration to adequately look at mortality with all treatment groups having a mortality rate of 1% or less. In the 52-week TONADO 1 and TONADO 2 studies, mortality rates were also quite low, with no treatment group exceeding 2%, and no overall differences were seen between TIO/OLO 5/5 mcg, TIO 5 mcg, and OLO 5 mcg. In terms of health care resource utilization, none of the included studies reported the proportion of patients requiring emergency department visits and hospital admissions. All studies reported the frequency of COPD exacerbations experienced by patients in addition to reporting the frequency of COPD exacerbations that required hospitalization (i.e., severe exacerbations). Similar to the mortality

assessments, the six- and 12-weeks studies were too short in duration to adequately ascertain any differences in COPD exacerbations between treatment groups, and studies were not designed to assess these differences. In the 52-week TONADO 1 and TONADO 2 studies, exacerbations were assessed as an additional efficacy end point, and annual rates per patient-year were found to be slightly lower in the TIO/OLO 5/5 mcg group than the TIO 5 mcg and OLO 5 mcg groups, although statistical significance was reached only in TONADO 2 for the comparison between TIO/OLO 5/5 mcg versus OLO 5 mcg (descriptive statistics). A manufacturer-sponsored, 52-week, phase 3, parallel-group randomized controlled trial is currently in progress (DYNAGITO, Study 1237.19) to assess the effect of TIO/OLO 5/5 mcg versus TIO 5 mcg in reducing the rate of moderate to severe COPD exacerbations.[35]

FEV_1 is a widely used measure to assess the efficacy of drug treatments for COPD in current clinical trials.[36] Trough FEV_1 was measured in all of the included trials, but was a primary end point only in TONADO 1 and TONADO 2 and a secondary end point in OTEMTO 1 and OTEMTO 2. There was a statistically significant increase in trough FEV_1 from baseline to week 24 in TONADO 1 and TONADO 2, and to end of treatment in the other studies, in the TIO/OLO 5/5 mcg group versus the monotherapies, placebo, and FP/SAL. The results generally exceeded the clinically significant threshold of 0.10 L for the comparisons between TIO/OLO 5/5 mcg and placebo, but not for the comparisons between TIO/OLO 5/5 mcg and the monotherapy groups, or TIO/OLO 5/5 mcg and the FP/SAL groups. However, according to the clinical expert consulted for this review, there is uncertainty regarding what the MCID for LAMA/LABA combination therapies versus monotherapy comparisons should be. Similar results were seen in the change from baseline in FEV_1 AUC outcomes when measured from 0 to 3 hours (TONADO 1, TONADO 2, OTEMTO 1, and OTEMTO 2), 0 to 12 hours (VIVACITO and ENERGITO), 12 to 24 hours (VIVACITO and ENERGITO), and 0 to 24 hours (VIVACITO and ENERGITO) after dosing. Of most interest were the FEV_1 $AUC_{0–24h}$ end points assessed in VIVACITO and ENERGITO, as TIO/OLO 5/5 mcg is a long-acting bronchodilator therapy.

Dyspnea as measured by the TDI focal score was assessed in TONADO 1 and TONADO 2 at week 24 and in OTEMTO 1 and OTEMTO 2 at week 12. Results were not consistent across the TONADO 1 and TONADO 2 trials, with a statistically significantly greater improvement in mean TDI focal score seen only in TONADO 1 for TIO/OLO 5/5 mcg compared with the monotherapy groups (not in testing hierarchy). In OTEMTO 1 and OTEMTO 2, there was a statistically significantly greater improvement in mean TDI focal score at week 12 for TIO/OLO 5/5 mcg compared with placebo. These studies also reported the proportion of TDI responders, which was defined as having a TDI focal score of at least one, corresponding to reported MCIDs (see APPENDIX 4: VALIDITY OF OUTCOME MEASURES). In TONADO 1, the rates of TDI responders were slightly greater in the TIO/OLO 5/5 mcg group compared with the monotherapy groups. In TONADO 2, there were no differences in responder rates between groups. In OTEMTO 1 and OTEMTO 2, there was a greater proportion of TDI responders in the TIO/OLO 5/5 mcg group compared with the placebo groups. Dyspnea was measured using the modified Borg scale in the exercise endurance studies (MORACTO 1, MORACTO 2, and TORRACTO) during cycle ergometry as the slope of intensity of breathing discomfort and an improvement in dyspnea was seen for TIO/OLO 5/5 mcg compared with placebo, but this was only statistically significant in MORACTO 1 and MORACTO 2. Therefore, it appears that there is an improvement in dyspnea with TIO/OLO 5/5 mcg compared with placebo, but the improvement over the monotherapies was less consistent.

Health-related quality of life was another key efficacy outcome, and COPD patients expressed a desire for improved quality of life with any new treatment (see APPENDIX 1: PATIENT INPUT SUMMARY). SGRQ total score was assessed as an additional end point at week 24 in TONADO 1 and TONADO 2, and as a primary end point at week 12 in OTEMTO 1 and OTEMTO 2. In TONADO 1 and TONADO 2, SGRQ total

score at week 24 was also considered a primary end point for a pre-specified pooled analysis of the two trials and was included in the statistical testing hierarchy to meet European Medicine Agency requirements. However, CDR generally places less emphasis on the pooled analysis as compared with the individual trials, as per Health Canada and the FDA.[31] SGRQ results were not consistent between TONADO 1 and TONADO 2, while the pre-specified pooled analysis showed a statistically significant difference in improvement from baseline at week 24 with the TIO/OLO 5/5 mcg group compared with the monotherapies. In OTEMTO 1 and OTEMTO 2, there was a statistically significantly greater improvement from baseline in SGRQ total score at week 12 in the TIO/OLO 5/5 mcg group compared with the placebo groups. All of these studies also reported the proportion of SGRQ responders, defined as an improvement of at least 4 points from baseline, corresponding to the MCID (see APPENDIX 4: VALIDITY OF OUTCOME MEASURES). Overall, there were a greater proportion of SGRQ responders in the TIO/OLO 5/5 mcg group compared with the monotherapy and placebo groups. Therefore, it appears that there is an improvement in SGRQ total score with TIO/OLO 5/5 mcg compared with placebo, but the improvement over the monotherapies was less consistent.

Exercise endurance as an outcome may be better correlated with quality of life and more applicable to real-life activity. Patients expressed a desire for higher energy levels and more independence in day-to-day living (see APPENDIX 1: PATIENT INPUT SUMMARY). Exercise endurance was evaluated in MORACTO 1, MORACTO 2, and TORRACTO as the endurance time at end of treatment during cycle ergometry at 75% maximal work capacity two hours post-dose. Patients with an endurance time of at least 25 minutes at baseline or training were excluded from these studies. The clinical expert consulted for this review noted that patients who would be able to complete at least 25 minutes of cycling at 75% maximal work capacity would be relatively fit. In all the exercise endurance studies, there was a statistically significant increase in exercise endurance time during cycle ergometry at end of treatment for the TIO/OLO 5/5 mcg group compared with placebo, but generally not compared to the monotherapy groups. Differences may not have been seen between TIO/OLO 5/5 mcg and the monotherapy groups due to the relatively short duration of the studies. The differences seen between TIO/OLO 5/5 mcg and placebo appeared to be clinically significant according to a suggested MCID for endurance time of 65 seconds (see APPENDIX 4: VALIDITY OF OUTCOME MEASURES). However, there are no widely accepted MCIDs, and tests may have been conducted using different parameters. TORRACTO also conducted an endurance shuttle walk test sub-study where the endurance time during a walk test at a speed corresponding to 85% of predicted peak oxygen consumption was assessed, but no statistically significant differences were seen between TIO/OLO 5/5 mcg and placebo. Therefore, it appears that there is an improvement in EET with TIO/OLO 5/5 mcg compared with placebo, but this improvement is not seen compared with the monotherapy groups. A manufacturer-sponsored, 12-week, phase 3, parallel-group, randomized controlled trial is currently in progress (PHYSACTO; Study 1237.16) to assess the effect of TIO/OLO 5/5 mcg versus TIO 5 mcg and placebo, with or without exercise training on top of behavioural modification, in improving exercise endurance.[37]

Lung volumes are of particular interest for patients with COPD and, similar to endurance time, are believed to have a stronger correlation with activity limitations compared with trough FEV_1.[38,39] In the exercise endurance studies, lung volume was measured by inspiratory capacity at rest before cycle ergometry at end of treatment, and results suggested an improvement from baseline with the use of TIO/OLO 5/5 mcg compared with the monotherapy components and placebo.

Other efficacy end points included the use of rescue medication, which was assessed in TONADO 1, TONADO 2, OTEMTO 1, and OTEMTO 2 as the number of puffs of daytime and nighttime rescue medication required per day compared with baseline. The baseline use of nighttime rescue medication

was nearly twice that of daytime rescue medication use. In TONADO 1 and TONADO 2, there was a greater decrease in the mean number of puffs per day of daytime and nighttime rescue medication on week 52 compared with baseline with TIO/OLO 5/5 mcg compared with TIO 5 mcg. In OTEMTO 1 and OTEMTO 2, there was a greater decrease in the mean number of puffs per day of daytime and nighttime medication on week 12 compared with baseline with TIO/OLO 5/5 mcg compared with placebo. However, as a common baseline mean was calculated rather than a baseline mean for each treatment group, it is unclear whether there would have been differences between groups at baseline that may have impacted the results.

ENERGITO was the only included study that compared TIO/OLO 5/5 mcg with an ICS/LABA combination therapy, FP/SAL 500/50 mcg and FP/SAL 250/50 mcg. The clinical expert consulted for this review noted that a stepwise treatment algorithm is recommended by current guidelines, with ICS/LABA combinations appropriate only if a LAMA/LABA combination is insufficient to alleviate symptoms or prevent exacerbations. However, clinicians do not always adhere to this recommended treatment algorithm, and ICS/LABA combination therapies are often prescribed earlier, inappropriately. Results from ENERGITO suggest that there is a greater improvement in FEV_1 outcomes with TIO/OLO 5/5 mcg compared with FP/SAL 500/50 mcg and FP/SAL 250/50 mcg, but the difference between TIO/OLO 5/5 mcg and the FP/SAL groups in trough FEV_1 did not exceed the clinically significant threshold of 0.10 L. However, there is uncertainty regarding what the MCID for LAMA/LABA versus ICS/LABA combination therapies should be.

There was no direct evidence available to assess the efficacy of TIO/OLO 5/5 mcg versus other LAMA/LABA combination therapies in the included studies. The manufacturer submitted a network meta-analysis (NMA) to compare the efficacy and safety of TIO/OLO 5/5 mcg with other LAMA/LABA fixed-dose combination therapies currently on the market, including aclidinium/formoterol 400/12 mcg (ACL/FM), indacaterol/glycopyrronium 110/50 mcg, and umeclidinium/vilanterol 62.5/25 mcg. Comparative efficacy and safety were based on a measure of trough FEV_1, SGRQ total score, TDI focal score, COPD exacerbations, and discontinuations due to an AE. There were 76 studies that met eligibility criteria for inclusion in the NMA, and outcomes data were analyzed for 24/26 weeks and 48/52 weeks where possible to allow for inclusion of more studies. The results of the NMA suggested that there is no statistically significant difference in outcomes between TIO/OLO 5/5 mcg and the other LAMA/LABA fixed-dose combination therapies. However, there was clinical heterogeneity among the included studies due to the inclusion of studies with outcomes measured at different time points in the same networks and differing inclusion criteria between included studies. Moreover, there was limited information provided as to how the various sources of heterogeneity were identified and accounted for in the NMA. Hence, the overall results of the NMA, in combination with the aforementioned limitations, indicate that there is no clear evidence of clinically relevant differences with respect to the outcomes associated with TIO/OLO and other LAMA/LABAs in the treatment of COPD.

The TIO/OLO 5/5 mcg fixed-dose combination is administered using the Respimat soft mist inhaler, which differs from dry powder inhalers where patients must place a capsule from a blister package into the inhaler before crushing and inhaling the powder. After inserting the cartridge and priming, the soft mist inhaler is prepared for use without the need for opening and loading individual capsules each time. However, each inhaler provides only 30 doses, and a new inhaler is required for each cartridge, which may have environmental implications as the cartridges are not currently recycled. In terms of patient preferences, two small observational studies suggested that patients preferred the use of the Respimat inhaler over the dry powder HandiHaler, but due to methodological limitations of the studies, this will need to be further evaluated (see APPENDIX 5: COMPARISON OF INHALER DEVICES). The clinical expert

consulted for this review noted that all inhalers work well if used correctly, and thorough education of the patient is an important step in ensuring proper use.

4.2.2 Harms

Generally, the overall incidence of AEs between treatment groups was similar, with slightly higher rates in the placebo groups. The most common AEs were COPD exacerbations and nasopharyngitis. The incidence of SAEs was generally low with no consistently observable differences between TIO/OLO 5/5 mcg and the monotherapy groups and placebo. The incidence of withdrawals due to adverse events (WDAEs) was also generally low, with a higher proportion of patients in the placebo groups withdrawing due an adverse event compared with the other treatment groups. In the 52-week TONADO 1 and TONADO 2 studies, there were higher proportions of patients who experienced AEs, SAEs, and WDAEs compared with the other studies due to the longer duration.

Notable harms were highlighted based on the anticholinergic and beta-agonist components of TIO/OLO. Anticholinergic and beta-agonist drugs may be associated with cardiovascular AEs. There were no long-term safety data beyond one year of use for TIO/OLO 5/5 mcg, which would be relevant for the evaluation of cardiovascular AEs. However, patients with a history of cardiovascular disorders were not enrolled in the studies, which may limit generalizability to the population of COPD patients with concomitant cardiovascular comorbidities. In the Health Canada–approved product monograph, there is a note that Inspiolto Respimat should be used with caution in patients with cardiovascular disorders due to cardiovascular effects seen with anticholinergic drugs.[24] In the included studies, the incidence of cardiovascular AEs was low, with the most common one being hypertension.

Other notable harms associated with anticholinergic drugs include dry mouth, dizziness, urinary retention, pyrexia, and blurred vision; however, these were rare across all treatment groups of the included studies. Cases of pneumonia, a safety issue associated with COPD, were also rare across study groups and trials. A safety issue associated with LABA use is an increased risk of asthma-related death,[24] as described in a warning in the Health Canada–approved product monograph. Hence, TIO/OLO 5/5 mcg is indicated only for the treatment of COPD. Patients expressed a desire for an increased ability to fight infections with new treatments (see APPENDIX 1: PATIENT INPUT SUMMARY). The incidences of infections such as nasopharyngitis and URTIs were generally balanced across treatment groups within studies.

There is no direct evidence to assess the safety of TIO/OLO 5/5 mcg versus other LAMA/LABA combination therapies in the included study. The manufacturer-submitted NMA did assess discontinuations due to AEs at 48/52 weeks as an outcome, but there was a lack of eligible studies in this network and only a comparison between TIO/OLO 5/5 mcg and indacaterol/glycopyrronium 110/50 mcg was assessed, which suggested that there were no statistically significant differences in discontinuation rates due to an AE.

4.3 Potential Place in Therapy[2]

There are currently no disease-modifying drugs available for the therapy of COPD. Bronchodilators thus remain the mainstay of therapy for symptomatic patients with COPD. Based on the Canadian Thoracic Society guidelines[11] and the GOLD guidelines,[13] long-acting inhaled bronchodilators are convenient and more effective at producing maintained symptom relief than short-acting bronchodilators. Long-acting

[2] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

inhaled bronchodilators reduce exacerbations and related hospitalizations and improve symptoms and health status. Combining bronchodilators of different pharmacological classes may improve efficacy and decrease the risks of adverse effects compared with increasing the dose of a single bronchodilator.

There are currently five combinations of an inhaled $beta_2$ agonist and anticholinergic drug that have been approved for the treatment of COPD. Although no head-to-head comparative study has been performed at this time, the submitted NMA suggests that TIO/OLO is as effective as the other once-per-day or twice-per-day combinations of an inhaled $beta_2$ agonist and anticholinergic, albeit noting the several limitations of this analysis.

One cannot make a diagnosis of COPD based on symptoms alone. The diagnosis of COPD still relies on the measurement of pulmonary function. However, once COPD is diagnosed, a stepwise approach to therapy is recommended.[11,13] TIO/OLO, like other combinations of a LABA and LAMA, should be considered in patients with COPD who remain symptomatic while employing either a LAMA or a LABA.

5. CONCLUSIONS

Ten manufacturer-sponsored, double-blind, phase 3 randomized controlled trials comparing TIO/OLO 5/5 mcg with its individual monocomponents, placebo, or FP/SAL met inclusion criteria for this review. Overall, the evidence was limited for key outcomes such as mortality, health care resource utilization, and COPD exacerbations, largely because the studies were not designed to assess these. There were statistically significant improvements in lung function with TIO/OLO 5/5 mcg compared with the monocomponents, placebo, and FP/SAL as measured by trough FEV_1 at week 24 in TONADO 1 and TONADO 2 and at the end of treatment for the other studies. Health-related quality of life as assessed by SGRQ total score were not consistent between TONADO 1 and TONADO 2, with only TONADO 1 reporting statistically significant improvements from baseline at week 24 with TIO/OLO 5/5 mcg compared with the monotherapy components. Results from the exercise endurance studies demonstrated an improvement in exercise endurance time during cycle ergometry with TIO/OLO 5/5 mcg compared with placebo but not compared with the monotherapy groups. The most common AEs in the included trials were nasopharyngitis and COPD exacerbations. SAEs and WDAEs were generally low and balanced between treatment groups, with a slightly higher rate of WDAEs in the placebo groups. The frequencies of cardiovascular effects, anticholinergic effects, and cases of pneumonia with TIO/OLO 5/5 mcg were very low, in part a reflection of the short duration of most of the studies. No data beyond 52 weeks were available. A manufacturer-submitted NMA suggested no difference in efficacy between TIO/OLO 5/5 mcg and other LAMA/LABA combination therapies with respect to trough FEV_1, SGRQ total score, TDI focal score, COPD exacerbations, and discontinuations due to AEs at 24/26-week and/or 48/52-week time points. However, there was clinical heterogeneity among the included studies due to the inclusion of studies with outcomes measured at different time points in the same networks and differing inclusion criteria between included studies. Hence, there is no clear evidence of clinically relevant differences with respect to the outcomes associated with TIO/OLO and other LAMA/LABAs in the treatment of COPD.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group Supplying Input

The Ontario Lung Association is a charitable organization whose mandate is to advocate for and provide programs and services to patients and health care providers while being the voice and primary resource in the prevention and control of respiratory illness. The Association has received sponsorships and grants to support educational and research initiatives from AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Pfizer, Roche, and Rx&D. In addition, they have received program funding from the Ontario Home Respiratory Services Association.

No conflicts of interests were declared with regard to the preparation of this submission.

2. Condition-Related Information

The information for all of the remaining sections was gathered though 11 online surveys sent to patients with chronic obstructive pulmonary disease (COPD), their caregivers, and their physicians. In addition, three phone interviews were conducted, input from a certified respiratory educator was obtained, and responses from previous surveys were also used. The information provided encompasses a cross-Canada perspective.

While everyday activities are impacted in all patients with COPD, the most troublesome were reported as shortness of breath, cough (with or without mucus), and fatigue. These were followed closely by wheezing and exercise limitation. Inability to fight infections and exacerbations leading to decreases in lung function were both highlighted as problematic and frustrating, in some cases leading to problems with travel (e.g., developing infections while away and having to curtail plans). Everyday activities such as opening doors, getting the mail, using stairs, carrying groceries, housework, cooking, and showering are often affected, leading to shortness of breath and fatigue. In addition, many of the aforementioned activities and daily routines take longer due to the symptoms and often require assistance from caregivers and family members. Patients experience frustration, depression, and a lack of hope at their inability to perform their daily tasks, having to rely on assistance, decreasing their physical and leisure activities, their ability (or lack thereof) to work, and their loss of independence. As expressed by one patient, “It is a constant fight to maintain independence and reduce depression. Each plateau you reach means adjustments, and the inability to earn an income means having to ‘make do’ all the time.” There is also apprehension at having to take the constant additional medications needed to fight infections and the potential need for supplemental oxygen.

Caregivers often feel the burden associated with COPD and its consequences. Work, relationships with family and friends, physical and leisure activities, and independence are affected while caring for the COPD patient as caregivers are relied upon to provide assistance for trips to appointments and have to undertake many of the household responsibilities.

3. Current Therapy-Related Information

Pharmacological treatments previously used by interviewed patients included Spiriva, Advair, Symbicort, Daxas, prednisone, Ventolin, Atrovent, Serevent, Seebri, and Onbrez. While some fatigue, shortness of breath, cough, low energy, and the inability to fight infections have been alleviated by current treatments, there remains hope that potentially more symptom resolution may be possible with newer

treatments. Some of the notable side effects with current treatments include dry mouth, mouth sores, increased choking while eating, vision problems, urinary issues, and adverse impacts on mood. In addition, many of these patients are on numerous concomitant medications and are therefore uncertain which side effect is produced by any specific medication.

The increased burden associated with the numerous medical appointments remains one of the issues that patients hope to have resolved with some of the new treatments. In addition, patients hope for less of the cost burden associated with these medications, as many are not covered by specific drug plans. Patients ultimately feel that current therapies do not reduce their mucus production enough, keep oxygen levels high enough, or increase their energy enough. Patients did report that following an exercise regime did help them manage their disease and did provide some improvements in breathing, but they still require further medical assistance.

4. Expectations About Inspiolto Respimat

Patients would like to experience reduced shortness of breath, reduced cough, reduced fatigue, and improved appetite with the newer treatments. In addition, they would prefer to have an increased ability to fight infections, higher energy levels, an improved quality of life, more independence, and fewer hospital admissions. While patients were willing to accept some side effects, they were not willing to experience anything worse than what they were currently experiencing, nor anything irreversible. Most patients also indicated that they did not want to travel to receive new treatments, make additional changes to their daily routines, or have those assisting them have to take additional time off work. Finally, patients and their caregivers would like less of a cost burden with newer treatments.

Only one patient had experience with Inspiolto Respimat. This patient had an improved appetite and no side effects, but rated Inspiolto Respimat as “worse than” in the area of time to accommodate treatment.

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:	July 3, 2015
Alerts:	Weekly search updates until November 18, 2015.
Study Types:	No search filters were applied
Limits:	No language or date limits 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
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
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.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-STRATEGY DATABASE	
#	**Searches**
1	(Spiolt* or Stiolt* or Inspiolt*).ti,ot,ab,sh,hw,rn,nm.
2	(1589477-29-1 or "1589477291").rn,nm.
3	1 or 2
4	(tiotropium* or Spiriva or BA679BR or BA 679BR or BA 679 BR).ti,ot,ab,sh,hw,rn,nm.
5	(139404-48-1 or "0139404481").rn,nm.
6	4 or 5
7	(olodaterol* or Striverdi or BL1744 or BL 1744 or Bi1744 or Bi-1744).ti,ot,ab,sh,hw,rn,nm.
8	(869477-96-3 or "0869477963").rn,nm.
9	7 or 8
10	6 and 9
11	3 or 10
12	11 use pmez
13	olodaterol plus tiotropium bromide/
14	(Spiolt* or Stiolt* or Inspiolt*).ti,ab.
15	13 or 14
16	*tiotropium bromide/
17	(tiotropium* or Spiriva or BA679BR or BA 679BR or BA 679 BR).ti,ab.
18	16 or 17
19	*olodaterol/
20	(olodaterol* or Striverdi or BL1744 or BL 1744).ti,ab.
21	19 or 20
22	18 and 21
23	15 or 22
24	23 use oemezd
25	24 not conference abstract.pt.
26	12 or 25
27	remove duplicates from 26

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:	June 29, 2015
Keywords:	Drug name, Indication
Limits:	No language or date 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: DETAILED OUTCOME DATA

TONADO 1 and TONADO 2: Additional Outcomes

TABLE 42: ADDITIONAL EFFICACY OUTCOMES — 52-WEEK PARALLEL-GROUP STUDIES (TONADO 1, TONADO 2)

Outcome	TONADO 1 (1237.5)			TONADO 2 (1237.6)		
	TIO/OLO 5/5 mcg (N = 522)	TIO 5 mcg (N = 527)	OLO 5 mcg (N = 528)	TIO/OLO 5/5 mcg (N = 507)	TIO 5 mcg (N = 506)	OLO 5 mcg (N = 510)
FEV_1 $AUC_{0–3h}$ response (L), week 52[a]						
N	474	454	451	502	500	507
Common baseline mean (SE)	1.158 (0.010)			1.150 (0.010)		
Adjusted mean response (SE)[b]	0.237 (0.009)	0.122 (0.009)	0.096 (0.009)	0.237 (0.010)	0.124 (0.010)	0.105 (0.010)
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	0.115 (0.090 to 0.139)	0.141 (0.117 to 0.166)	-	0.112 (0.086 to 0.139)	0.132 (0.105 to 0.158)
Trough FEV_1 response (L), week 52[a]						
N	521	520	519	497	498	503
Common baseline mean (SE)	1.161 (0.010)			1.150 (0.010)		
Adjusted mean response (SE)[b]	0.099 (0.009)	0.036 (0.009)	0 (0.009)	0.093 (0.009)	0.040 (0.009)	0.011 (0.009)
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	0.064 (0.039 to 0.088)	0.100 (0.075 to 0.124)	-	0.053 (0.027 to 0.079)	0.081 (0.055 to 0.108)
SGRQ total score, week 52						
N	502	487	483	478	468	471
Common baseline mean (SE)	43.182 (0.356)			43.844 (0.376)		
Adjusted mean (SE)	36.700 (0.558)	37.104 (0.570)	39.187 (0.576)	37.549 (0.584)	38.096 (0.593)	38.781 (0.596)
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	−0.404 (−1.969 to 1.160)	−2.488 (−4.061 to −0.915)	-	−0.547 (−2.181 to 1.086)	−1.232 (−2.869 to 0.404)

AUC = area under the curve; CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; MD = mean difference; MMRM = mixed model for repeated measures; OLO = olodaterol; SE = standard error; SGRQ = St. George's Respiratory Questionnaire; TIO = tiotropium; vs. = versus.

[a] Not included in the hierarchical testing sequence, therefore considered descriptive.

[b] MMRM including treatment, planned test day, treatment-by-test-day interaction, baseline, and baseline-by-test-day interaction as fixed effects, and patient as random effect.

[c] Subset of patients with 12h pulmonary function tests.

Source: Clinical Study Reports.[1,2]

TABLE 43: ADDITIONAL EFFICACY OUTCOMES — POOLED ANALYSES OF 52-WEEK PARALLEL-GROUP STUDIES (TONADO 1, TONADO 2)

Outcome	TONADO 1 (1237.5) and TONADO 2 (1237.6)		
	TIO/OLO 5/5 mcg	TIO 5 mcg	OLO 5 mcg
SGRQ total score, week 24, *primary end point (pooled)*			
N	979	954	954
Common baseline mean (SE)	43.512 (0.259)		
Adjusted mean response (SE)[b]	36.674 (0.386)	37.907 (0.393)	38.366 (0.396)
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	−1.233 (−2.313 to −0.153)	−1.693 (−2.778 to −0.608)
P value	-	0.0252	0.0022
Responder, n (%)	563 (57.5)	465 (48.7)	427 (44.8)
TDI focal score, week 24, *secondary end point (pooled)*			
N	992	978	984
Common baseline mean (SE)	6.544 (0.031)		
Adjusted mean response (SE)[b]	1.983 (0.095)	1.627 (0.096)	1.564 (0.096)
Adjusted MD (95% CI), TIO/OLO vs. comparator	-	0.356 (0.092 to 0.619)	0.420 (0.155 to 0.684)
P value	-	0.0082	0.0019
Responder, n (%)	545 (54.9)	495 (50.6)	474 (48.2)

CI = confidence interval; MD = mean difference; OLO = olodaterol; SE = standard error; SGRQ = St. George's Respiratory Questionnaire; TIO = tiotropium; vs. = versus.

APPENDIX 4: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity and the minimal clinically important difference (MCID) of the following outcome measures:

- forced expiratory volume in one section (FEV_1)
- St. George's Respiratory Questionnaire (SGRQ)
- transition dyspnea index (TDI)
- exercise endurance time (EET)
- modified Borg scale

Findings

FEV_1, SGRQ, TDI, EET, and the modified Borg scale are briefly summarized in Table 44.

TABLE 44: VALIDITY AND MINIMAL CLINICALLY IMPORTANT DIFFERENCE OF OUTCOME MEASURES

Instrument	Type	Evidence of Validity	MCID[a]	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, or a change of 5% to 10% from baseline	Cazzola 2008[40] Jones 2014[41]
SGRQ	SGRQ is a disease-specific measure of HRQoL that consists of 50 items with 76 responses, was developed for patients with chronic airflow limitation. 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 indicates greatest impairment.	Yes	4 units	Jones 1992[42] Leidy 2010[43] Meguro 2007[44] Maly 2006[45]
TDI	TDI is used to measure dyspnea and consists of 24 items measuring 3 categories: functional impairment, magnitude of task, and magnitude of effort. Items are rated in 7 grades ranging from −3 (major deterioration) to +3 (major improvement), where lower scores indicate more deterioration in the severity of dyspnea from baseline.	Yes	1 unit	American Thoracic Society[46]
EET	EET was measured using the ESWT, which is a standardized constant-paced field test for the assessment of endurance	Unknown	70 s (95% CI, 46 to 95) 65 secs (95%	Brouillard 2008[47] Eaton 2006[48] Brouillard 2007[49] Troosters 2013[50]

Instrument	Type	Evidence of Validity	MCID[a]	References
	capacity in patients with chronic lung disease.		CI, 45 to 85)	Pepin 2011[51]
Modified Borg Scale	11-point scale (ranges 0 [no dyspnea] to 10 [max dyspnea] points)	Yes	1 unit	Crisafulli[52] Kendrick[53] Belman[54] Mador[55] Ries[56]

CI = confidence interval; EET = exercise endurance time; ESWT = enhanced shuttle walk test; FEV_1 = forced expiratory volume in 1 second; HRQoL = health-related quality of life; MCID = minimal clinically important difference; SGRQ = St. George's Respiratory Questionnaire; TDI = transition dyspnea index.
[a] MCID has not been determined between two active treatment groups.

One-Second Forced Expiratory Volume

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.[36,57] In clinical practice, FEV_1 is used to grade risk of death in COPD patients.[58] The generally accepted clinically important change in FEV_1 is between 0.10 L and 0.14 L, or a change of 5% to 10% from baseline.[40,41] Previous research indicated that relative change rather than absolute change may be more meaningful in patients with worse airflow limitation.[41] There is evidence that for patients who are undergoing a COPD exacerbation, a two-day increase of 0.10 L reduced the relative risk of treatment failure by 20%.[57] A systematic review published in 2011 investigated the relationship between change in FEV_1 and patient-reported outcomes using data from randomized controlled trials of long-acting bronchodilator therapy.[59] Findings suggested that change in trough FEV_1 was negatively correlated with change in SGRQ total score: 0.10 L increase in trough FEV_1 was associated with a statistically significant reduction of 2.5 units in SGRQ total score, while a 4.0-unit change in SGRQ total score was related to 0.16 L increase in FEV_1. Change in FEV_1 had weak associations with TDI and COPD exacerbations: a 0.10 L increase in FEV_1 was associated with 0.5 unit improvement in TDI, or 6% reduction in the proportion of patients experiencing at least one exacerbation.

While both pre-bronchodilator and post-bronchodilator FEV_1 values have been reported to be indicators of health status, risk of death, and level of COPD severity, 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.[58] Predictors of mortality were analyzed. While FEV_1, body mass index, 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 than pre-bronchodilator per cent predicted FEV_1 ($P = 0.009$ versus 0.131).

St. George's Respiratory Questionnaire

SGRQ is a disease-specific measure of health-related quality of life that was specifically developed for patients with airway obstruction.[42] 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 health-related quality of life.[60] The instrument has been used worldwide in studies and in clinical settings.[60]

SGRQ 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 questionnaire contains 50 items and 76 weighted responses that are divided into three subscales: symptoms (eight items measuring the frequency of respiratory symptoms over a preceding period that may range from one month to one year), activity (16 items measuring the disturbances to the patient's daily physical activity), and impacts (26 items measuring the psychosocial impact of the disease).[45,62,63] Items are weighted using empirically derived weights in order to determine SGRQ total score, which ranges from 0 to 100, where 0 indicates no impairment and 100 indicates worst possible health.[44,45] The generally accepted MCID for a change in total SGRQ from baseline is 4.0 units, and a decrease in score indicates an improvement in HRQL.[43,63] In the manual of the SGRQ-C questionnaire (a shorter version of SGRQ that was developed using COPD data only and is specific to patients with COPD), an MCID of 4.0 units is used for the within-group comparison as well as the between-group comparison.[64] The SGRQ manual does not indicate whether the MCID of 4.0 units can be used in the between-group comparison. However, it is reasonable to use this threshold to determine the clinical significance of the differences between groups of patients.

Component scores for the symptoms, activity, and impacts 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 (wheeze, breathlessness, cough, etc.) on a 5-point scale, where the low scores indicate no symptoms and high scores indicate more severe symptoms.[45] A number of items in the symptoms component relate to the frequency of symptoms over the previous year.[65] Responses on the other two domains are mostly yes-or-no in nature. The activity domain deals with mobility and physical activity problems that either cause or are limited by breathlessness.[45] Social functioning and psychosocial disturbances have been identified by patients as particularly troubling aspects of COPD. Impacts covers aspects involved in social functioning and psychosocial disturbances resulting from the obstructive airways disease (employment, panic, medication, and side effects).[65]

Transition Dyspnea Index

The TDI is an interviewer-administered, multidimensional instrument used to measure the severity of dyspnea.[46,66] It was developed by Mahler et al. in 1984. When used to determine breathlessness in patients at baseline it is called the baseline dyspnea index (BDI). TDI measures changes in dyspnea severity from the baseline as established by the BDI. Both BDI and TDI consist of 24 items in three categories: functional impairment, magnitude of task, and magnitude of effort (assessed in BDI), and the changes in functional impairment, magnitude of task, and magnitude of effort from baseline (assessed in TDI). At baseline, dyspnea is rated by items in BDI in five grades ranging from 0 (severe) to 4 (unimpaired). The ratings for each category are added to form a baseline focal score ranging from 0 to 12, with a lower score indicating more severe dyspnea. At the transition period, changes in dyspnea are assessed by TDI. Items are rated by seven grades ranging from −3 (major deterioration) to +3 (major improvement). The ratings for each of the three categories are added to form a total TDI score ranging from −9 to +9. A lower TDI score indicates greater severity of dyspnea. Both indices have been validated in patients with respiratory disease. Acceptable responsiveness (ability to detect change) and construct validity (a change in TDI correlates with changes in other variables such as the 12-minute walking test, FEV_1, and SGRQ scores) of BDI and TDI were demonstrated in previous clinical trials.[67] A one-unit change in TDI was considered to be the MCID.[46]

Exercise Endurance Time

The European Medicines Agency (EMA) stated that when lung function is selected as a primary end point, a co-primary end point (such as assessment of exercise capacity) should be evaluated to provide additional evidence of efficacy.[68] In the included studies of the current review, endurance walking capacity or EET was measured in the endurance shuttle walk test. This is a standardized constant-paced field test for the assessment of endurance capacity in patients with chronic lung disease. It was found to be responsive to bronchodilation and rehabilitation therapies in COPD patients.[47,48]

Before each endurance shuttle walk test, patients received standardized instructions to walk for as long as possible, although there was a predetermined 20-minute maximum. No encouragement should be provided during the test to avoid a potential confounding effect on exercise performance. The test was performed in an enclosed corridor on a flat, 10-metre-long course. The course was identified by two cones, each positioned 0.5 metres from either end to allow patients to walk in an oval and thereby avoid the need for abrupt changes in direction. After a 90-second warmup, the patient's walking speed was set at the speed corresponding to 80% of the peak oxygen consumption as predicted by an incremental shuttle walking test at baseline.[47] During the endurance shuttle walk test, patients were instructed to walk up and down the course, turning around the cones at either end. The end of the test was determined by one of the following: the patient felt that he or she could not maintain the required speed, the patient failed to complete a shuttle in the time allowed, or the study coordinator found it was necessary to discontinue due to safety reasons related to patient complaints. The number of shuttles was counted, but the most important measure was the time that the patient walked. EET is expressed in seconds.

There are no widely accepted MCIDs for EET during the endurance shuttle walk test. Previous research suggested a difference of 70 seconds (95% confidence interval [CI], 46 to 95 seconds) as a clinically important difference for within-patient comparisons of EET.[49] A difference of 65 seconds (95% CI, 45 to 85 seconds) was suggested as an MCID for EET in more recent clinical studies.[51]

Modified Borg Dyspnea Scale

The modified Borg dyspnea score is a categorical scale from 0 to 10, where 0 represents no dyspnea and 10 represents maximal dyspnea.[52] It is obtained at the end of exercise endurance testing and reflects the maximum degree of dyspnea at any time during the test. Although it is a subjective assessment scale for assessing the intensity of breathlessness, it has been shown to be reliable for quantifying dyspnea in trial patients with COPD who have undergone a six-minute treadmill walk test.[51,54,55] The MCID has been estimated to be one unit.[56]

Summary

FEV_1, SGRQ, and TDI have all been shown to be valid outcome measures for patients with COPD. The suggested MCIDs for FEV_1, SGRQ, and TDI were 0.1 to 0.14 L, 4 units change from baseline, and 1 unit change from baseline, respectively.

In patients with COPD, exercise testing is useful to assess the degree of impairment, the prognosis, and the effects of interventions. Exercise capacity was measured using EET in this review along with other clinical outcomes such as lung function improvements. No information on the validation of this outcome measure was reported. A difference of 70 seconds, or 65 seconds based on more recent evidence, was considered acceptable as an MCID for within-patient comparisons of EET.

APPENDIX 5: COMPARISON OF INHALER DEVICES

Aim

To compare patient preferences for inhaler devices along with the efficiency of inhaler technique between the Respimat soft mist inhaler and other inhaler devices (including dry powder inhalers and pressurized metered dose inhalers) for patients diagnosed with COPD. The evidence for the summary was not systematically reviewed.

Findings

Trial and Patient Characteristics

Two references were identified that compared patient preference and satisfaction for inhaler devices,[69,70] ease of use,[69,70] rate of wrong steps,[69] perception of correct technique,[69] and favourite device for daily use.[69] Details of patient characteristics for the aforementioned studies are provided in Table 45.

The study by Chorao et al.[69] was a cross-sectional observational study of 301 adult patients (464 devices) with asthma (n = 194 [64%]) or COPD (n = 107 [35%]) currently using inhaler devices who were attending outpatient clinics in a Portuguese tertiary university hospital. Patients not using the most commonly used inhaler devices in Portugal (Aerolizer, Autohaler, Breezhaler, Diskus, HandiHaler, metered dose inhaler without spacer, Miat-Haler, Novolizer, Respimat, and Turbohaler) were excluded from the trial, as were those who could not read or write. A questionnaire used to evaluate the perception of the patient's inhaler technique, their satisfaction with said device, and their perception of whether their wishes were taken into account when the physician was prescribing their inhaler devices was completed first. This was followed immediately by a face-to-face interview, during which patients demonstrated their inhaler technique. Checklists based on the manufacturer specifications were used to evaluate the patient's competency with their inhaler technique. Once the demonstration was completed, the investigator explained the proper technique for the patient's inhaler and further demonstrated the proper technique for the other devices. Patients subsequently tested all of the inhalers using the proper technique and were then asked which device was the easiest to use, their preferred device for daily use, and the reasons for their decision.[69] While the study questionnaire was not officially validated, it was pre-tested in 12 patients. It was found to be readable and easy to understand, and uniformity was maintained by only one interviewer performing all interviews.[69]

The Hodder and Price study[70] examined inhaler satisfaction and preference between the Respimat soft mist inhaler and either pressurized metered dose inhalers or dry powder inhalers using the validated Patient Satisfaction and Preference Questionnaire.[70] They identified one open-label crossover study wherein 224 patients diagnosed with asthma and COPD used both the Respimat soft mist inhaler (ipratropium plus fenoterol) and a hydrofluoroalkane pressurized metered dose inhaler for seven weeks each. The outcome measures of interest included patient satisfaction and preference as measured by the Patient Satisfaction and Preference Questionnaire. This study was industry-funded. While two additional studies comparing the Respimat soft mist inhaler with dry powder inhalers were also identified, one solely examined patients with moderate to severe asthma (looking at comparative preference of the Respimat soft mist inhaler compared with the Turbohaler) and thus is not described further.[70] The other comparative study was a four-week, open-label observational study comparing patient satisfaction and preference with the Respimat soft mist inhaler (ipratropium bromide plus fenoterol) and the Diskus dry powder inhaler (corticosteroid plus long-active beta-adrenoceptor agonist) in 150 patients with COPD and asthma.[70] The outcome measure of interest included patient preference

as measured by the mean difference of the total Patient Satisfaction and Preference Questionnaire score.[70] This observational study was also industry funded. [70]

Patient Satisfaction and Preference Questionnaire

The Patient Satisfaction and Preference Questionnaire, which was developed by psychometric testing experts (with input from patients and clinical experts) to independently ascertain preference for any type of respiratory device or treatment, has been field tested and found valid and reliable when examining patients with COPD and asthma.[70] It consists of a self-administered questionnaire that contains 15 total items, of which 13 are satisfaction items, one is a preference item, and one pertains to being willing to continue using the device in question. Part 1 consists of the 13 satisfaction items, which are rated using a 7-point Likert scale (1 = very dissatisfied to 7 = very satisfied) and which are partitioned into one of two domains: performance or convenience. Part 2 consists of stand-alone questions: one question examines inhaler preference and has three possible answers (prefer inhaler 1, prefer inhaler 2, or no preference), and the other question explores the patient's willingness to continue the device (each inhaler was given a score ranging between 0 and 100, with a higher value indicating more willingness to continue). The minimum important difference was included in the validation and has been determined to be a 10-point difference between devices for all scores (performance, convenience, and total satisfaction scores).[70]

TABLE 45: TRIAL AND PATIENT CHARACTERISTICS

	Chorao et al., 2014[69]	Hodder and Price, 2009[70]	
		Respimat SMI[a] vs. HFA MDI Trial	Respimat SMI[a] vs. DPI (Diskus)[b]
Trial Characteristics			
Trial type	Cross-sectional Portuguese observational study	Randomized OL crossover study	Observational study
Duration	4 months	7 + 7 weeks	4 weeks
Patient Characteristics			
N	301	224	150
Diagnosis	COPD or asthma[c]	COPD, asthma, or both[c]	COPD or asthma[c]
Age (years), mean (SD)		NR	NR
< 45	90 (30)	-	-
45 to 64	132 (44)	-	-
> 64	79 (26)	-	-
Females, n (%)	181 (60)	NR	NR
Years of education, n (%)		NR	NR
1 to 4	138 (46)	-	-
5 to 9	67 (22)	-	-
10 to 12	62 (21)	-	-
> 12	34 (11)	-	-
Number of inhalers, n (%)		NR	NR
1	166 (55)	-	-

	Chorao et al., 2014[69]	Hodder and Price, 2009[70]	
2	108 (36)	-	-
≥ 3	27 (9)	-	-

COPD = chronic obstructive pulmonary disease; DPI = dry powder inhaler; HFA = hydrofluoroalkane; NR = not reported; OL = open-label; MDI = metered dose inhaler; SD = standard deviation; SMI = soft mist inhaler; vs. = versus.
[a] Ipratropium plus fenoterol.
[b] Usually corticosteroid plus long-acting beta-adrenoceptor agonist.
[c] Results not separated out per indication.

Outcomes

In the Chorao et al. study, the Turbohaler and Diskus devices were observed to be the most widely used, while the Breezhaler and Respimat soft mist inhaler (among others) represented < 5% of devices in use.[69] In addition, patients with COPD in this study were more likely to use the HandiHaler and Diskus devices (26% and 21%, respectively, of total COPD devices).[69] Median scores were high and generally similar with regard to both self-evaluation of inhaler technique (ranging from 86 to 97, with the exception of the Miat-Haler and Autohaler at 59 and 62, respectively) and satisfaction with current device (ranging from 79 to 96, with the exception of the Miat-Haler and Autohaler at 62 and 50, respectively). The Turbohaler was identified as the easiest device to use (21%) along with being the favourite device for daily use (17%), while the Breezhaler, Handilhaler, and Respimat soft mist inhaler followed (see Table 46). Patient reasons for choosing a device as a favourite for daily use included the device's physical characteristics (30%), practicality (26%) and ease of use (26%), and what the patient was accustomed to using (18%).[69]

No consensus regarding inhaler device preference or ease of use was reported in the Chorao et al.[69] study. In addition, no device was reported to have superior performance technique.[69] Higher rates of wrong steps were observed in females (when compared with males, $P < 0.001$), in patients with lower education levels (when comparing one to four years versus > 12 years, $P = 0.001$), and in older individuals (when comparing > 64 years of age to ≤ 64 years of age, $P < 0.001$).[69] The odds ratio of rate of wrong steps with regard to inhaler devices was observed to be higher in the HandiHaler than either the Respimat soft mist inhaler or the Breezhaler (termed as "Other") when compared with the Turbohaler (adjusted odds ratio 3.71 [95% CI, 1.38 to 10.02] and 0.97 [95% CI, 0.43 to 2.18]).[69] No other items (e.g., duration of use, perception of correct technique, etc.) correlated with the rate of wrong steps (data not shown). Detailed outcomes[69] are provided in Table 46.

TABLE 46: SELECTED OUTCOMES FROM THE CHORAO ET AL.[69] STUDY

Outcome Description	Inhaler Devices[a]			
	Turbohaler	HandiHaler	Respimat SMI	Breezhaler
Easiest device to use, %	21	5	4	5
Daily use favourite, %	17	6	6	7
Motives for choosing daily use device, n (%)				
Accustomed (18%)	27 (44)	5 (26)	2 (10)	2 (7)
Ease of use (26%)	9 (14)	4 (21)	4 (21)	6 (21)
Practical (26%)	15 (24)	7 (37)	7 (37)	5 (17)
Physical characteristics (30%)	11 (18)	3 (16)	6 (32)	16 (55)
Presence of error in inhaler technique, OR (95% CI)				
Inhaler Device[b]				
Crude OR[c]	Reference	3.47 (1.37 to	0.86 (0.40 to 1.82)[d]	

Outcome Description	Inhaler Devices[a]			
	Turbohaler	HandiHaler	Respimat SMI	Breezhaler
		8.79)		
Adjusted OR[e]	Reference	3.71 (1.38 to 10.02)	0.97 (0.43 to 2.18)[d]	

CI = confidence interval; OR = odds ratio; SD = standard deviation; SMI = soft mist inhaler.
[a] Although many inhalers were prominent in Portugal — Aerolizer, Autohaler, Breezhaler, Diskus, HandiHaler, MDI without spacer, Miat-Haler, Novolizer, Respimat, and Turbohaler – this review was concerned only with those included in the table.
[b] Using the Turbohaler as the reference.
[c] Univariate logistic regression analysis.
[d] Multivariate logistic regression analysis.
[e] Includes all inhalers except Aerolizer, Diskus, MDI, HandiHaler, and Turbohaler (reference).

Hodder and Price[70] reported a statistically significantly higher percentage of patients who preferred the Respimat soft mist inhaler when compared with the hydrofluoroalkane pressurized metered dose inhaler (72.3% and 17.4%, respectively, $P < 0.001$). Neither age nor the presence of comorbidities that had the potential to affect inhaler handling influenced these preferences (data not provided). Mean satisfaction scores between the two inhalers were similar; however, the total Patient Satisfaction and Preference Questionnaire score was both statistical significant and reached the minimum important difference (10.8 points) in favour of the Respimat soft mist inhaler when compared with the hydrofluoroalkane pressurized metered dose inhaler due to the Respimat soft mist inhaler scoring significantly higher in the performance domain of this tool.[69] When ranked using a 100-point scale at the end of the study (0 refers to "not willing" and 100 refers to "definitely willing"), patients were more willing to continue with the Respimat soft mist inhaler when compared with the hydrofluoroalkane pressurized metered dose inhaler (median scores of 85 and 50, respectively, $P < 0.001$).[69] In the second study they identified that, comparing the Respimat soft mist inhaler with the Diskus dry powder inhaler, the mean scores for the performance domain, the convenience domain, and the total Patient Satisfaction and Preference Questionnaire score were statistically significantly higher with the Respimat soft mist inhaler; however, these were not clinically significant.[70] Preferences were also higher for the Respimat soft mist inhaler when compared with the Diskus (63.5% and 33.8%, respectively), while 2.7% expressed no preference.[70] Detailed outcomes[70] are provided in Table 47.

TABLE 47: OUTCOMES FROM THE HODDER AND PRICE[70] STUDY

Outcome Description	Inhaler Devices		
	HFA MDI	Respimat SMI[a]	DPI (Diskus)[b]
Respimat SMI vs. HFA MDI			
Preference for inhaler (%)	17.4	72.3	-
P value	< 0.001		-
Satisfaction			
Total PASAPQ score	72.9	83.7	-
Mean difference (SD)	10.8[c] (20.3)		-
P value	< 0.001		-
Respimat SMI vs. DPI (Diskus)			
Preference for inhaler (%)[d]	-	63.5	33.8
Willingness to continue,[e] median	-	85	50
P value for median difference		< 0.001	

Outcome Description	Inhaler Devices		
	HFA MDI	Respimat SMI[a]	DPI (Diskus)[b]
Satisfaction			
Total PASAPQ score	-	80.2	75.5
Mean difference (SD)	-	4.7 (NR)	
P value	-	0.001	

DPI = dry powder inhaler; HFA = hydrofluoroalkane; NR = not reported; MDI = metered dose inhaler; PASAPQ = Patient Satisfaction and Preference Questionnaire; SD = standard deviation; SMI = soft mist inhaler; vs. = versus.
[a] Ipratropium bromide plus fenoterol.
[b] Usually corticosteroid plus long-acting beta-adrenoceptor agonist.
[c] Met requirement for minimal clinically important difference.
[d] 2.7% had no preference for inhaler type.
[e] Measured using a 0 to 100 scale, where 0 = not willing and 100 = definitely willing.

Critical Appraisal

One of the main issues with both studies[69,70] was the absence of observations made per the patient indication. For this reason, results cannot be generalized solely to the patient with COPD, as the results were not partitioned according to individual patient indication (COPD or asthma) or combined indications (COPD and asthma). Another important caveat to both studies[69,70] is the possibility that the medication contained in each inhaler type influenced the satisfaction results. While the Patient Satisfaction and Preference Questionnaire[70] helps to minimize some of the potential bias (as it is specifically designed to assess the inhaler attributes along with being self-administered, thereby mitigating assessor bias), differences in bronchodilator efficacy, the onset speed, and medication tolerability may all affect the patient's satisfaction with the device.

In the Chorao et al.[69] study, not all devices were compared with regard to rate of wrong steps due to their infrequent use in this population (including the Breezhaler and Respimat soft mist inhaler). In addition, past training, or a lack thereof, was not assessed, making it difficult to ascertain whether specific or in-depth education regarding inhaler use affected the patient's ability to successfully use their device. The fact that this study was a single-centre, single-country study that excluded illiterate patients also potentially limits the generalizability of the results in addition to not being able to fully exclude selection bias.

In the Hodder and Price[69] article, both of the included studies were industry funded. In addition, one of the authors stated that he had received honorariums, fees, and research grants from the manufacturer who produced the Respimat soft mist inhaler.[70]

Summary

While the Chorao et al.[69] study did not provide evidence regarding any single preferred, easier to use, or technically superior device, the authors reported that performing errors were more predominant in females, elderly patients, and those using the Aerolizer and HandiHaler devices. Hodder and Price[70] reported both statistically and clinically significant higher total Patient Satisfaction and Preference Questionnaire scores in patients using the Respimat soft mist inhaler when compared with the hydrofluoroalkane pressurized metered dose inhaler. This statistical significance remained when comparing the Respimat soft mist inhaler with the Diskus dry powder inhaler; however, these results did not reach clinical significance. One caveat in both of these studies includes the observation that none of the results were partitioned according to patient indication; therefore, one cannot necessarily generalize to the patient with only COPD.

APPENDIX 6: SUMMARY OF INDIRECT COMPARISONS

Introduction

Background

The objective of this review is to summarize and critically appraise any indirect comparisons of the tiotropium bromide monohydrate/olodaterol hydrochloride (TIO/OLO) fixed-dose combination 5/5 mcg to other treatments of interest for the treatment of chronic obstructive pulmonary disease (COPD). Other than ENERGITO (TIO/OLO versus fluticasone propionate/salmeterol), there are no trials with direct head-to-head comparisons between TIO/OLO 5/5 mcg and other combination long-acting muscarinic agonist/long-acting beta$_2$ agonist (LAMA/LABA) and inhaled corticosteroid (ICS)/LABA treatments for moderate to severe COPD. Hence, indirect comparisons that include TIO/OLO 5/5 mcg allow one to glean information on the comparative efficacy and safety of this LAMA/LABA combination versus other active treatments for COPD.

Methods

A network meta-analysis (NMA) submitted by the manufacturer was summarized and critically appraised.[71] In addition, a literature search was undertaken to identify any additional relevant published indirect comparisons.

Description of Indirect Comparisons Identified

No additional relevant published NMAs were identified in the literature search.

Review and Appraisal of Indirect Comparisons

Review of Manufacturer-Submitted NMA

Objectives and rationale for manufacturer-submitted network meta-analysis

The NMA was conducted in order to determine the relative clinical benefit of TIO/OLO 5/5 mcg compared with other treatments of interest (Table 48) for patients with moderate to very severe COPD.

TABLE 48: INTERVENTIONS CONSIDERED IN THE NETWORK META-ANALYSIS

LAMA/LABA (Decision Set)	Comparator Set
Fixed-Dose Combinations ACL/FM IND/GLY TIO/OLO UMEC/VI *Free-Dose Combination* TIO + SAL TIO + FM	Placebo TIO

ACL = aclidinium; FM = formoterol; GLY = glycopyrronium; IND = indacaterol; LABA = long-acting beta$_2$ agonist; LAMA = long-acting muscarinic antagonist; OLO = olodaterol; SAL = salmeterol; TIO = tiotropium; UMEC = umeclidinium; VI = vilanterol.

Methods for manufacturer-submitted network meta-analysis

Study eligibility and selection process

The inclusion criteria for the systematic literature review are presented in Table 49.

TABLE 49: INCLUSION CRITERIA FOR THE SYSTEMATIC LITERATURE REVIEW

Population	Adult patients ≥ 18 years of age with COPD
Interventions	**LAMA/LABA FDC**: TIO/OLO, IND/GLY, UMEC/VI, ACL/FM **ICS/LABA FDC (+/– LAMA):** BEC/FM, BUD/FM, FP/SAL, FF/VI **LAMA + LABA free-dose combination:** TIO + SAL, TIO + OLO **LAMA monotherapy:** TIO
Comparators	Any of the interventions above or placebo
Outcomes	• Pulmonary function (trough FEV_1, FEV_1 AUC) • TDI focal score, TDI responders • Hospitalizations • COPD exacerbations • Discontinuations • SGRQ total score, SGRQ responders
Study Design	RCTs ≥ 12 weeks duration, systematic literature reviews (with or without a meta-analysis)

ACL = aclidinium; AUC = area under the curve; BEC = beclomethasone dipropionate; BUD = budesonide; COPD = chronic obstructive pulmonary disease; FDC = fixed-dose combination; FEV_1 = forced expiratory volume in 1 second; FF = fluticasone furoate; FM = formoterol; FP = fluticasone propionate; GLY = glycopyrronium; ICS = inhaled corticosteroid; IND = indacaterol; LABA = long-acting $beta_2$ agonist; LAMA = long-acting muscarinic antagonist; OLO = olodaterol; RCT = randomized controlled trial; SAL = salmeterol; SGRQ = St. George's Respiratory Questionnaire; TDI = transition dyspnea index; TIO = tiotropium; UMEC = umeclidinium; VI = vilanterol.

To identify relevant studies for this NMA, a systematic search of the literature was performed to identify randomized controlled trials that met the eligibility criteria in Table 49. The literature was searched in multiple databases on September 11, 2014, using predefined search strategies. There were no time restrictions on the search, and the search was restricted to English language only. Additional hand searches were conducted to capture data related to clinical trials not yet published (i.e., conference abstracts, clinical trial registries, health technology assessment websites, regulatory authorities' websites). Titles and abstracts of studies were screened by two independent reviewers, and discrepancies were resolved by discussion. Potentially relevant articles were reviewed in full-text and assessed for inclusion. Studies were excluded if abstracts were not available and no further information could be retrieved based on the citation.

Following the systematic literature review, studies were assessed for inclusion in the NMA, and the following exclusion criteria were applied to determine which studies to use for data extraction:

- results for outcomes of interest not reported in the following ranges: 20 to 28 weeks or 48 to 52 weeks, in order to mitigate heterogeneity
- results for studies looking at TIO and placebo, which allowed use of concomitant LABAs, as concomitant LABA use would not be allowed in the main LAMA/LABA comparators of interest
- studies conducted exclusively in Asian patients, as there may be differences in treatment effect
- post-hoc or pooled analyses of studies already extracted unless reporting a subgroup of interest
- studies looking at interventions not in the decision or comparator set in Table 48 (i.e., TIO plus OLO free combination, ICS/LABA combinations).

Data extraction

Data extraction was conducted by two independent reviewers and quality checked by a third reviewer.

Comparators

The comparators of interest for the NMA included the LAMA/LABA fixed-dose combinations currently available: aclidinium/formoterol (ACL/FM), indacaterol/glycopyrronium (IND/GLY), and umeclidinium/vilanterol (UMEC/VI). In addition, TIO + salmeterol (SAL) as a free-dose combination was included as a comparator of interest. TIO monotherapy and placebo were included as comparators in order to link the networks for the meta-analysis. Although no specific doses were specified in the inclusion criteria, results were reported only for Health Canada–approved doses: TIO/OLO 5/5 mcg, ACL/FM 400/12 mcg, IND/GLY 110/50 mcg, UMEC/VI 62.5/25 mcg, TIO 5 mcg Respimat inhaler, TIO 18 mcg dry powder inhalation with the HandiHaler, and SAL 50 mcg. Although ICS/LABA combinations were included in the systematic literature review, these were not considered in the decision set (Table 48) and therefore were not included in the NMA.

For the base-case analysis, data from the TIO 5 mcg (Respimat) and TIO 18 mcg (HandiHaler) groups were combined in order to create connected networks for all outcomes of interest. One randomized controlled trial found that were was no statistically significant differences in treatment effect between these two formulations.[72]

Outcomes

The following outcomes with a description of the definition were analyzed in the NMA: trough forced expiratory volume in one second (FEV_1) response, transition dyspnea index (TDI) focal score, percentage of TDI responders (TDI ≥ 1), St. George's Respiratory Questionnaire (SGRQ) total score, percentage of SGRQ responders (≥ 4-point improvement from baseline), moderate to severe COPD exacerbations, severe COPD exacerbations, all-cause discontinuations, and discontinuation due to an adverse event (AE). FEV_1 area under the curve (AUC) outcomes were not analyzed due to inconsistencies in measurements across studies.

For the included outcomes, the time points extracted ranged from 20 to 28 weeks and 48 to 52 weeks. These ranges were chosen as most studies had durations of 24/26 or 48/52 weeks. A time point of 24/26 weeks was chosen as the primary outcome for the analyses because the primary end points in TONADO 1 and TONADO 2, the pivotal trials for TIO/OLO 5/5 mcg, were measured at week 24. If there were two or more time points in a study that were in the range of interest, preference was given to time points for which more data were available or which were closer to the majority of time points of other studies in the network.

There were differences across studies in the definition of a COPD exacerbation and the time of assessment of COPD exacerbations. Only studies that defined a COPD exacerbation as follows were included in the network: worsening of two or more respiratory symptoms with a duration of three or more days requiring specified treatment changes, with a moderate exacerbation requiring additional treatment with antibiotics, systemic glucocorticoids, or both, and a severe exacerbation requiring hospitalization. Studies were excluded if they had no definition or a different definition of COPD exacerbations and if they reported data at a time point outside the range of interest. This excluded 40% of studies reporting moderate to severe exacerbations and 30% of studies reporting severe exacerbations from those respective networks.

Quality assessment of included studies

A quality assessment of individual studies was performed using the Cochrane Collaboration's tool for assessing risk of bias.[73] Possible biases considered were randomization, allocation concealment, baseline

characteristics, blinding, attrition, outcomes, and whether an intention-to-treat analysis was used. Responses to the questions were categorized as high risk, low risk, or unclear risk of bias.

Evidence network

Evidence networks were provided for each outcome for 24/26 weeks and 48/52 weeks, where applicable. Evidence networks were also provided for each sensitivity analysis conducted. Due to the volume of networks, results are presented narratively below.

Indirect comparison methods

An NMA was deemed the most appropriate analysis due to the complexity of the evidence networks, the multiple studies per comparison, and at least one closed loop in the networks. Fixed-effects and random-effects Bayesian network meta-analyses were conducted and compared treatments of interest using odds ratios for binary outcomes or mean treatment difference for continuous outcomes with associated 95% credible intervals. Outcomes measured at 24/26 weeks and 48/52 weeks were pooled together. All baseline and intervention effect parameters were given uninformative normal (0, 1000) priors and between-study standard deviation (SD) flat uniform distributions with an appropriately large range given the scale of measurement. All analyses involved a 50,000 run-in iteration phase and a 50,000 iteration phase for parameter estimation.

Both fixed effects and random effects models were fitted, but meta-regression was performed only using a random effects model, because the aim is to assess the extent to which between-study heterogeneity impacts observed treatment effects. Meta-regression was performed by controlling for post-bronchodilator per cent FEV_1 predicted at baseline and concomitant ICS use at baseline for the analysis of trough FEV_1. Model fit was assessed using the deviance information criterion (DIC) and total residual deviance was reported. Convergence was confirmed by visual inspection of density, history, and auto-correlation plots. If auto-correlation was observed, chains were thinned until auto-correlation was no longer present.

To further assess effect modification, Bucher comparisons were conducted for all networks containing closed loops that did not contain multi-group trials. Values for omega, a measure of the conflict between the direct and indirect effect sizes in the network, were reported.

Data on missing standard errors (SEs) associated with the change in continuous outcomes from baseline were imputed using methods described in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 using available SDs.[73] In cases where only *P* values were available and no confidence intervals, SDs, and SEs were reported, it was assumed that the *P* values were calculated using a Wald test (for normally distributed variables), and the SE was determined by rearranging the equation. If *P* values were reported as $P < 0.001$, the *P* value was assumed to be 0.001.

Three sensitivity analyses (SA) were conducted:

- SA1: analysis of SGRQ and TDI outcomes using data from the individual TONADO 1 and TONADO 2 studies instead of pooled data
- SA2: analysis using separate TIO 5 mcg (Respimat inhaler) and TIO 18 mcg (HandiHaler) doses instead of pooled data of these doses
- SA3: the inclusion of one study conducted in Asian patients only (ARISE) for the outcome of trough FEV1 at 24/26 weeks.

Results

Study characteristics

A total of 145 publications were identified from the systematic literature review. After applying additional exclusion criteria, 76 studies were included in the NMA. A summary table was provided in the report, which included information on interventions and comparators, inhaler devices used, and assessment time points. However, there was no table or description summarizing patient demographics and disease characteristics for individual studies. A table summarizing study and patient baseline characteristics of studies used in the NMA was provided later by the manufacturer. The mean age across studies was similar, but the proportion of patients who were current smokers ranged from 59.4% to 51.5% in studies that reported this characteristic. The proportion of patients who were using ICS at baseline ranged from 21.1% to 75.5%, and disease severity of enrolled patients also varied widely between studies. The majority of studies (> 80%) were associated with low or unclear risk of bias, while some studies were associated with high risk of bias in terms of allocation concealment and blinding, which may be due to the high number of studies that included open-label TIO.

Potential sources of heterogeneity and inconsistency were investigated by analyzing effect modifiers, including COPD severity, use of concomitant ICS, and history of exacerbations, for studies included in the analysis for trough FEV_1. For COPD severity, the distribution of GOLD stages and post-bronchodilator per cent FEV_1 predicted at baseline were assessed. The distribution of GOLD stages II, III, and IV at baseline was reported in 15 studies included in the analysis for trough FEV_1, with the average distribution across studies being 51% GOLD stage II, 41.9% GOLD stage III, and 6.8% GOLD stage IV. One study (SPARK, IND/GLY 110/50 mcg versus TIO 18 mcg) was conducted in patients with GOLD stage III and stage IV only, while five studies were conducted in patients with GOLD stage II and stage III only. Post-bronchodilator per cent FEV_1 predicted at baseline was reported in 16 studies and averaged 50.9% with a relatively uniform distribution across studies. The SPARK study reported a slightly lower value (< 40%), which may reflect the more severe patients that were enrolled in this study.

For COPD exacerbation history, 10 studies used in the analysis for trough FEV_1 reported the proportion of patients who experienced none or at least one exacerbation in the 12 months prior to enrolment. The distribution of patients who experienced none or at least one exacerbation in the 12 months prior to enrolment were relatively uniform across the 10 studies, with an average distribution of 59.1% for patients with no exacerbations and 40.8% of patients with at least one exacerbation. The outlier was the SPARK study, where nearly all patients experienced at least one exacerbation.

The use of concomitant ICS at baseline was reported in 18 studies included in the analysis for trough FEV_1. The proportion of patients using concomitant ICS at baseline was widely variable across studies, with an average of 48.2% (range < 20% to > 70%). The study with the highest proportion of patients on concomitant ICS at baseline was the SPARK study.

Network meta-analysis results

Only results for the random-effects analysis are presented here, as it may be more appropriate due to the heterogeneity across included trials. Results for the fixed-effects analysis were similar, though the credible intervals were narrower. In addition, only results for TIO/OLO 5/5 mcg versus TIO monotherapy and the other fixed-dose LAMA/LABA combinations are presented, as these are the most relevant comparators. In all networks, LAMA/LABA combinations were linked through placebo or TIO monotherapy and not directly to one another. The 52-week TONADO 1 and TONADO 2 studies comparing TIO/OLO 5/5 mcg to TIO 5 mcg were included in all networks.

Change from baseline in trough forced expiratory volume in one second

For the change from baseline in trough FEV_1 at 24/26 weeks, 14 studies were included in the network. For the change from baseline in trough FEV_1 at 48/52 weeks, 10 studies were included in the network. At 24/26 weeks and 48/52 weeks, the change in trough FEV_1 was statistically significantly greater in TIO/OLO 5/5 mcg compared with TIO monotherapy (Table 50). At 24/26 weeks, there was no statistically significant difference between TIO/OLO 5/5 mcg and ACL/FM 400/12 mcg, IND/GLY 110/50 mcg, and UMEC/VI 62.5/25 mcg in change from baseline in trough FEV_1. At 48/52 weeks, there was no statistically significant difference between TIO/OLO 5/5 mcg and IND/GLY 110/50 mcg in change from baseline in trough FEV_1.

TABLE 50: CHANGE FROM BASELINE IN TROUGH FORCED EXPIRATORY VOLUME IN ONE SECOND AT 24/26 WEEKS AND 48/52 WEEKS

TIO/OLO 5/5 mcg Versus Comparator[a]	Mean Treatment Difference [95% CrI]	
	24/26 Weeks	48/52 Weeks
TIO (5 mcg or 18 mcg)	[redacted]	[redacted]
ACL/FM 400/12 mcg	[redacted]	[redacted]
IND/GLY 110/50 mcg	[redacted]	[redacted]
UMEC/VI 62.5/25 mcg	[redacted]	[redacted]
DIC[b]	[redacted]	[redacted]

ACL = aclidinium; CrI = credible interval; DIC = deviance information criterion; FM = formoterol; GLY = glycopyrronium; IND = indacaterol; OLO = olodaterol; TIO = tiotropium; UMEC = umeclidinium; VI = vilanterol.
[a] Mean treatment difference > 0 favours TIO/OLO 5/5 mcg over comparator.
[b] For random effects analysis.

Change in St. George's Respiratory Questionnaire score from baseline

For the change from baseline in SGRQ score at 24/26 weeks, 16 studies were included in the network. For the change from baseline in SGRQ score at 48/52 weeks, six studies were included in the network. There were no statistically significant differences between TIO/OLO 5/5 mcg and TIO monotherapy, ACL/FM 400/12 mcg, IND/GLY 110/50 mcg, and UMEC/VI 62.5/25 mcg at 24/26 weeks in change from baseline in SGRQ score. There were also no statistically significant differences between TIO/OLO 5/5 mcg and TIO monotherapy and IND/GLY 110/50 mcg at 48/52 weeks.

TABLE 51: CHANGE FROM BASELINE IN ST. GEORGE'S RESPIRATORY QUESTIONNAIRE SCORE AT 24/26 WEEKS AND 48/52 WEEKS

TIO/OLO 5/5 mcg Versus Comparator[a]	Mean Treatment Difference [95% CrI]	
	24/26 Weeks	48/52 Weeks
TIO (5 mcg or 18 mcg)	[redacted]	[redacted]
ACL/FM 400/12 mcg	[redacted]	[redacted]
IND/GLY 110/50 mcg	[redacted]	[redacted]
UMEC/VI 62.5/25 mcg	[redacted]	[redacted]
DIC[b]	[redacted]	[redacted]

ACL = aclidinium; CrI = credible interval; DIC = deviance information criterion; FM = formoterol; GLY = glycopyrronium; IND = indacaterol; OLO = olodaterol; TIO = tiotropium; UMEC = umeclidinium; VI = vilanterol.
[a] Mean treatment difference < 0 favours TIO/OLO 5/5 mcg over comparator.
[b] For random effects analysis.

Transition Dyspnea Index focal score

For the TDI focal score at 24/26 weeks, 14 studies were included in the network. For the TDI focal score at 48/52 weeks, four studies were included in the network. There were no statistically significant differences between TIO/OLO 5/5 mcg and TIO monotherapy, ACL/FM 400/12 mcg, IND/GLY 110/50 mcg, and UMEC/VI 62.5/25 mcg at 24/26 weeks in TDI focal score. There were also no statistically significant differences between TIO/OLO 5/5 mcg and TIO monotherapy at 48/52 weeks.

TABLE 52: TRANSITION DYSPNEA INDEX FOCAL SCORE AT 24/26 WEEKS AND 48/52 WEEKS

TIO/OLO 5/5 mcg Versus Comparator[a]	Mean Treatment Difference [95% CrI]	
	24/26 weeks	48/52 Weeks
TIO (5 mcg or 18 mcg)	[redacted]	[redacted]
ACL/FM 400/12 mcg	[redacted]	[redacted]
IND/GLY 110/50 mcg	[redacted]	[redacted]
UMEC/VI 62.5/25 mcg	[redacted]	[redacted]
DIC[b]	[redacted]	[redacted]

ACL = aclidinium; CrI = credible interval; DIC = deviance information criterion; FM = formoterol; GLY = glycopyrronium; IND = indacaterol; OLO = olodaterol; TIO = tiotropium; UMEC = umeclidinium; VI = vilanterol.
[a] Mean treatment difference > 0 favours TIO/OLO 5/5 mcg over comparator.
[b] For random effects analysis.

Chronic obstructive pulmonary disease exacerbations

For moderate-to-severe exacerbations, eight studies were included in the network. For severe exacerbations, 12 studies were included in the network. There were no statistically significant differences in moderate-to-severe exacerbations between TIO/OLO 5/5 mcg and TIO monotherapy, IND/GLY 110/50 mcg, and UMEC/VI 62.5/25 mcg. There were also no statistically significant differences in severe exacerbations between TIO/OLO 5/5 mcg and TIO monotherapy, ACL/FM 400/12 mcg, IND/GLY 110/50 mcg, and UMEC/VI 62.5/25 mcg.

TABLE 53: CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATIONS

TIO/OLO 5/5 mcg Versus Comparator[a]	Mean OR [95% CrI]	
	Moderate-to-Severe Exacerbations	Severe Exacerbations
TIO (5 mcg or 18 mcg)	[redacted]	[redacted]
ACL/FM 400/12 mcg	[redacted]	[redacted]
IND/GLY 110/50 mcg	[redacted]	[redacted]
UMEC/VI 62.5/25 mcg	[redacted]	[redacted]
DIC[b]	[redacted]	[redacted]

ACL = aclidinium; CrI = credible interval; DIC = deviance information criterion; FM = formoterol; GLY = glycopyrronium; IND = indacaterol; OLO = olodaterol; OR = odds ratio; TIO = tiotropium; UMEC = umeclidinium; VI = vilanterol.
[a] An OR of < 1 favours TIO/OLO 5/5 mcg over comparator.
[b] For random effects analysis.

Discontinuations at 48/52 weeks

For all-cause discontinuations at 48/52 weeks, seven studies were included in the network. For discontinuations due to AEs at 48/52 weeks, nine studies were included in the network. There were no statistically significant differences in all-cause discontinuations and discontinuations due to an AE at 48/52 weeks between TIO/OLO 5/5 mcg and TIO monotherapy and IND/GLY 110/50 mcg.

TABLE 54: DISCONTINUATIONS AT 48/52 WEEKS

TIO/OLO 5/5 mcg Versus Comparator[a]	Mean OR [95% CrI]	
	All-Cause Discontinuations	Discontinuations Due to Adverse Event
TIO (5 mcg or 18 mcg)	[redacted]	[redacted]
IND/GLY 110/50 mcg	[redacted]	[redacted]
DIC[b]	[redacted]	[redacted]

CrI = credible interval; DIC = deviance information criterion; GLY = glycopyrronium; IND = indacaterol; OLO = olodaterol; OR = odds ratio; TIO = tiotropium.
[a] An OR of < 1 favours TIO/OLO 5/5 mcg over comparator.
[b] For random effects analysis.

Model fit
Both fixed-effects and random-effects analyses were presented, and model fit was assessed using DICs. The DIC values were similar for the fixed-effects and random-effects models, but were slightly lower for the fixed-effects model, possibly due to a fixed-effects model being the more parsimonious one. However, due to the heterogeneity seen across the included studies, a random-effects model may be more appropriate for this NMA.

Meta-regression
A mega-regression was performed to assess the impact of concomitant ICS use and disease severity (measured as post-bronchodilator per cent FEV_1 predicted at baseline) on treatment effect sizes in trough FEV_1. Only results for the 24/26-week analyses were provided, as convergence could not be achieved for the 48/52-week networks due to the insufficient number of studies. Results of the meta-regression were similar to the results from the base-case analyses, with a slight decrease in effect size.

Sensitivity analyses
The results of all three sensitivity analyses (SA1, SA2, and SA3) were similar to the base-case analyses.

Inconsistency
All networks that contained closed loops and no multi-group trials (trough FEV_1 24/26 weeks and 48/52 weeks, SGRQ score 24/26 weeks, TDI score 24/26 weeks, all-cause discontinuation) were assessed for consistency using the Bucher test, and values for omega were reported. A statistically significant value was found for omega ($P < 0.05$) in the change in SGRQ score from baseline at 24/26 weeks, indicating potential inconsistency in this network caused by the UMEC/VI trials.

Critical appraisal
The quality of the manufacturer-submitted indirect analyses was assessed according to the recommendations of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[74]

Limitations
There were several limitations with the conduct and reporting of this NMA. A free-dose combination of TIO plus FM was listed in the decision set but not included as an intervention in the selection criteria for the systematic literature review. It is unclear whether this was an error in reporting. Baseline characteristics across studies were not reported in detail, so it was unclear how included studies compared in terms of patient demographics, previous treatment history, smoking status, disease

severity, and number of patients enrolled. No subgroup analyses were performed that would investigate any heterogeneity due to differences in baseline characteristics. The manufacturer stated that subgroup analyses were not feasible due to the lack of access to patient-level data from all included studies. The number of studies included in the NMA was not reported descriptively.

Outcomes at time points of 24/26 weeks and 48/52 weeks were grouped together for all outcomes except for COPD exacerbations in order to allow for the inclusion of additional studies. Meta-regression was used to evaluate the extent to which the covariates of ICS use and disease severity accounted the heterogeneity of treat effects, but other covariates were not assessed. For the studies included in the COPD exacerbations network, there were marked differences between studies with regard to time of assessment, which is concerning as the risk of having an exacerbation depends on the observational period. TIO 5 mcg (Respimat) and TIO 18 mcg (HandiHaler) doses were pooled in order to generate connected networks, but this may not be an issue due to the similar efficacy of both formulations, and the results from SA2 that split the doses into separate nodes were similar to the base-case analyses. Results at 48/52 weeks were sparser than those at 24/26 weeks, giving less data for longer-term outcomes.

Potential effect modifiers such as COPD severity, concomitant ICS use, and exacerbation history were investigated, but only for the studies contributing to the change from baseline in trough FEV_1 analysis and not for any other analyses. Meta-regression analyses were performed for COPD severity and concomitant ICS use for change from baseline in trough FEV_1 at 24/26 weeks only. Assessments of inconsistency using the Bucher test found potential inconsistency in the change from SGRQ score from baseline at 24/26 weeks network caused by the UMEC/VI trials, but no sensitivity analyses were performed to investigate the effect of removing one or more of these studies. The manufacturer provided additional information detailing a sensitivity analysis that was run to assess the impact of removing one or more of the studies causing inconsistency, and the analysis did not change the overall conclusions.

The risk of bias was assessed for the studies included in the NMA, but the actual studies assessed to have a high risk of bias were not specified and it was unclear whether these were included in the networks and how they may have impacted the analyses. The manufacturer provided information on individual assessment of included studies with regard to allocation concealment and blinding, and inclusion of studies with a high risk of allocation concealment (due to administration of open-label TIO) was done in order to increase the evidence base for the comparisons.

Strengths

A systematic literature search was performed and a search strategy was provided to ensure the comprehensiveness and transparency of data retrieval, and the risk of bias of the included studies was assessed. The patient population of moderate to very severe COPD was relevant to the question at hand, and the interventions analyzed in the NMA included all relevant LAMA/LABA fixed-dose combination therapies at the appropriate Health Canada–approved doses. Most of the outcome measures assessed in the MTC were relevant and consistent with the key efficacy assessments included in the CADTH Common Drug Review (CDR) review, including COPD exacerbations and discontinuations due to AEs. In addition, the time points chosen for the outcomes of interest were an appropriately long duration (24/26 weeks and 48/52 weeks). The DIC was used to compare model fit between the fixed-effects and random-effects models.

Discussion

One manufacturer-submitted NMA was summarized and critically appraised. No other indirect comparisons were identified through an additional literature search. The objective of the manufacturer-submitted NMA was to compare the efficacy and safety of TIO/OLO 5/5 mcg to other treatments of interest for COPD. The comparators of interest were narrowed down in a decision set, which included the LAMA/LABA fixed-dose combination therapies currently on the market (ACL/FM, IND/GLY, UMEC/VI) and free-dose LAMA/LABA combinations of TIO with either SAL or FM. Placebo and TIO monotherapy were included only to connect the networks. Only results for the comparisons with TIO monotherapy and the LAMA/LABA fixed-dose combinations are presented in this review. The reason why ICS/LABA comparators were not included in the NMA is unclear, as they would be appropriate comparators for the treatment of moderate to severe COPD.

The NMA reported comprehensive eligibility criteria for study inclusion and included duplicate screening and data extraction when conducting the systematic literature review. Additional inclusion criteria were applied after the systematic literature review to determine the final studies that would be included in the NMA, and the risk of bias was assessed for the included studies. Baseline characteristics of individual trials were not reported, making it difficult to assess differences in patients enrolled across included studies. Potential effect modifiers including COPD severity, ICS use at baseline, and COPD exacerbation history were investigated for studies contributing to the trough FEV_1 analysis, but not for any other analysis. Synthesis of the included trials was performed through a Bayesian network meta-analysis, and both fixed-effects and random-effects models were used; the methodologies used were reported in great detail. Due to the heterogeneity across studies, only results for the random-effects model are presented here, despite DIC values suggesting that the fixed-effects model was a better fit. Results were similar for both random-effects and fixed-effects analyses, with slightly larger credible intervals associated with the random-effects analyses.

Outcomes were analyzed at 24/26 weeks and 48/52 weeks in order to include more trials in the respective networks and prevent too much heterogeneity. However, for the studies included in the COPD exacerbations networks, there was a large range of time points at which exacerbation data were extracted. This may affect the interpretation of the results, as the risk of having an exacerbation depends on the observation period. Three sensitivity analyses were performed, but none addressed the potential heterogeneity seen across included trials in the networks.

Conclusion

In the absence of head-to-head trials comparing TIO/OLO 5/5 mcg with other LAMA/LABA combination therapies for moderate to very severe COPD, the manufacturer conducted a Bayesian NMA based on a systematic literature review of randomized controlled trials to compare the efficacy and safety of TIO/OLO 5/5 mcg with other LAMA/LABA fixed-dose combination therapies (ACL/FM 400/12 mcg, IND/GLY 110/50 mcg, and UMEC/VI 62.5/25 mcg). Results suggested that TIO/OLO 5/5 mcg was not statistically different from ACL/FM 400/12 mcg, IND/GLY 110/50 mcg, and UMEC/VI 62.5/25 mcg in lung function (trough FEV_1), health-related quality of life (SGRQ questionnaire), dyspnea symptoms (TDI focal score), COPD exacerbations, and discontinuations due to AEs. However, there was clinical heterogeneity among the included studies due to the inclusion of studies with outcomes measured at different time points in the same networks and differing inclusion criteria between included studies. Moreover, there was limited information provided about how the various sources of heterogeneity were identified and accounted for in the NMA. Hence, the overall results of the NMA, in combination with the aforementioned limitations, indicate that there is no clear evidence of clinically relevant differences with respect to the outcomes associated with TIO/OLO and other LAMA/LABAs in the treatment of COPD.

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