Common Drug Review
Clinical Review Report

September 2017

Drug	umeclidinium/vilanterol (Anoro Ellipta) dry powder inhaler (DPI)
Indication	Indicated for 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	List in a similar manner to tiotropium, as a maintenance bronchodilator treatment for COPD.
Manufacturer	GlaxoSmithKline Canada Inc. (GSK)

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in respirology who provided input on the conduct of the review and the interpretation of findings.

Through the Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

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ABBREVIATIONS

AE	adverse event
BDI	Baseline Dyspnea Index
CDR	CADTH Common Drug Review
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CSR	Clinical Study Report
DB	double-blind
DPI	dry powder inhaler
EET	exercise endurance time
EQ-5D	EuroQol 5-Dimensions Questionnaire
ER	emergency room
ESWT	endurance shuttle walking test
FDC	fixed-dose combination
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
GOLD	Global Initiative for Obstructive Lung Disease
HRQoL	health-related quality of life
ICS	inhaled corticosteroids
ITT	intention-to-treat
L	litre
LABA	long-acting beta2-agonists
LAMA	long-acting muscarinic antagonist
LS	least squares
mcg	microgram
MCID	minimal clinically important difference
MD	mean difference
MMRM	mixed model repeated measures
NBLA	New Brunswick Lung Association
OLA	Ontario Lung Association
OR	odds ratio
PP	per-protocol population
RCT	randomized controlled trial
SABA	short-acting beta2-agonists
SAE	serious adverse event
SAMA	short-acting muscarinic antagonist
SGRQ	St. George's Respiratory Questionnaire
TDI	treatment dyspnea index
TIO	tiotropium
UMEC	umeclidinium bromide
VI	vilanterol trifenatate

EXECUTIVE SUMMARY

Introduction

Chronic obstructive pulmonary disease (COPD) is a respiratory disorder characterized by progressive, partially reversible airway obstruction and lung hyperinflation, systemic manifestations, and increasing frequency and severity of exacerbations.[1] There is overlap of COPD subtypes, with many individuals presenting with features of both chronic bronchitis and emphysema, as well as asthma, which differs fundamentally from COPD.[2] Although disease activity and the nature of symptomatic impairment may vary from patient to patient, cough, excess sputum production, and dyspnea are the typical symptoms of COPD.[3] Statistics Canada has reported that between 2009 and 2011, 4% of Canadians aged 35 years to 79 years self-reported being diagnosed with COPD.[4]

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.[5] Management decisions are guided by disease severity (i.e., symptoms or 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.[5] Bronchodilators form the mainstay of pharmacotherapy for COPD,[5] and include short-acting beta2-agonist (SABAs) and short-acting muscarinic antagonist (SAMAs) drugs. Long-acting beta2-agonist (LABA) or long-acting muscarinic antagonist (LAMA) drugs as well as combinations of fixed-dose LABAs and inhaled corticosteroids (LABA plus ICS) are the most commonly used treatments for COPD in Canada. Antimuscarinic and beta2-agonist drugs are often used in combination for maximal improvement in dyspnea and function.

Umeclidinium bromide ("umeclidinium") plus vilanterol trifenatate ("vilanterol") (Anoro Ellipta) is a LABA plus LAMA combination dry powder for oral inhalation bronchodilator product. The recommended dose of umeclidinium plus vilanterol is 62.5 mcg/25 mcg once daily.

Indication Under Review
Indicated for long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema.
Listing Criteria Requested by Sponsor
List in a similar manner to tiotropium, as a maintenance bronchodilator treatment for COPD.

The objective of this review is to evaluate the beneficial and harmful effects of umeclidinium plus vilanterol (UMEC/VI) for the maintenance treatment of patients with COPD, including chronic bronchitis and emphysema.

Results and Interpretation

Included Studies

Six studies met the inclusion criteria for this review. They were all phase 3 multi-centre, double-blind, (DB) randomized controlled trials (RCTs) in which once-daily UMEC/VI 62.5 mcg/25 mcg fixed-dose combination (FDC) oral inhaler formulation was compared with one or both of its individual components (UMEC 62.5 mcg or VI 25 mcg), and with either placebo or tiotropium (TIO) 18 mcg, all as once-daily monotherapy. Patient participants were adults (≥ 40 years) with an extensive smoking history and

diagnosed with moderate to severe COPD. Baseline characteristics among treatment groups were similar in each study. One trial (DB2113373, N = 1536) evaluated the safety and efficacy of UMEC/VI, UMEC 62.5 mcg, VI 25 mcg, and placebo over a 24-week period. Three other studies (DB2113360, N = 846; DB2113374, N = 872; and ZEP117115, N = 905) compared UMEC/VI 62.5 mcg/25 mcg with TIO 18 mcg over a 24-week period. Two additional studies (DB2114417, N = 349; and DB2114418, N = 308) were placebo-controlled, combination and component crossover trials that evaluated the effect of UMEC/VI, UMEC 62.5 mcg, VI 25 mcg, or placebo on exercise endurance time (EET) and trough FEV_1 following 12 weeks of treatment in patients with COPD. The main comparison in these studies was UMEC/VI versus placebo; comparisons of the combination versus the individual components were considered supportive only. Each study had two 12-week treatment periods that were separated by a 14-day washout period. Where it was used, TIO was administered through the HandiHaler device while all the other treatments were administered using the Ellipta device.

Although UMEC/VI 125 mcg/25 mcg and UMEC 125 mcg monotherapy were treatment groups in some studies, they were not included in this review because neither dose has a Health Canada indication for COPD.

Apart from the exercise endurance studies (DB2114417, DB2114418), the primary efficacy outcome for all other included studies (DB2113373, DB2113360, DB2113374, and ZEP117115) was trough FEV_1 on day 169, defined as the mean of the FEV_1 values obtained 23 hours and 24 hours after dosing on the last day of treatment (i.e., on day 168 of week 24). The exercise tolerance studies had post-dose EET and trough FEV_1 at week 12 as co-primary efficacy end points. The post-dose EET at week 12 was defined as the EET obtained three hours after dosing at week 12; and trough FEV_1 at week 12 was defined as the FEV_1 value obtained 24 hours after dosing on treatment day 84. Key secondary efficacy outcomes included dyspnea measured using Transition Dyspnea Index (TDI) and health-related quality of life (HRQoL) measured using St. George's Respiratory Questionnaire (SGRQ) and EuroQol 5-Dimensions Questionnaire (EQ-5D) scores. In all the studies, the analysis followed a step-down hierarchy such that unless a comparison that was higher in order demonstrated statistical significance, inference about statistical significance could not be made from lower order comparisons. The order in which comparison was made for each study has been described in the Statistical Analysis section of this report.

The main limitations of the studies included the fact that all were 24 weeks or shorter in duration, which is not likely a sufficient duration to assess key clinical outcomes such as mortality and mortality due to COPD. Furthermore, none of the studies was designed to evaluate treatment effects on COPD exacerbations. Patient groups expressed concern about COPD exacerbation, as this is associated with both short- and long-term consequences on overall health (APPENDIX 1). The TIO-controlled trials were reported as double-blinded and double-dummy studies; however, the investigators reported that although the TIO and placebo capsules were closely matched in colour, the blinding of TIO was imperfect because the TIO capsules had trade markings and the placebo capsules did not. Therefore, the DB may have been compromised in these studies. There was a substantial proportion of discontinuations (ranging as high as 20% to 27% in study DB2113373) across studies. Although there was no clear discontinuation differential among groups within studies (except those on placebo more frequently discontinued), there is a concern regarding the validity of the findings in view of frequencies of discontinuations that are this high. Finally, there were no head-to-head studies comparing UMEV/VI with other LABA/LAMA combinations.

Efficacy

Mortality or Mortality due to Chronic Obstructive Pulmonary Disorder

The overall rate of death was ≤ 1% and was similar among studies, except for the crossover exercise endurance trials. One of the exercise endurance studies (DB2114417) had no deaths reported in any of the treatment groups of interest to this review, while the other study reported a single death that occurred in the UMEC/VI group. Causes of death included COPD exacerbation or respiratory failure, cardiac arrest or failure, and cancer. With the exception of one event of sudden death in the VI treatment group of study DB2113373, none of the deaths was reported to be related to any study drug.

Health Care Resource Utilization

Outcomes evaluated under health care resource utilization included contact with health care provider, emergency room visits, and hospitalization, all of which were patient-reported. In all the included studies, reports of emergency room visits and hospitalization were small, and generally a difference in health care resource use was not observed among studies or among treatment groups.

Exacerbations

None of the studies was designed to assess comparative differences among treatments on COPD exacerbation. Patients who were hospitalized for COPD or pneumonia within 12 weeks prior to screening, which may have been attributed to a COPD exacerbation, were excluded from the study, and those who experienced exacerbation in the course of the study were to be withdrawn. In study DB2113373, on-treatment COPD exacerbations were reported in 12.5% of patients in the placebo group, 6.5% in the UMEC/VI group, and 7% to 9% in single component treatment groups. Just over 6% of patients treated with UMEC/VI were withdrawn due to COPD exacerbation compared with 12% in placebo. [redacted]

Generally, the rates of reported COPD exacerbation in the crossover studies were lower compared with the parallel-group studies. This is at least in part because the crossover studies had shorter durations and the patients had less severe symptoms in order to safely undergo exercise regimens versus the parallel design studies. A clear trend of withdrawals due to COPD exacerbation was not observed in studies comparing UMEC/VI with tiotropium. In two of the studies, COPD exacerbation led to more withdrawals from the UMEC/VI (6.3% and 11%) than the TIO group (4.9% and 5.6%), while a third study reported a higher rate of withdrawal due to COPD exacerbation in the TIO-treated group (6.4%) compared with the UMEC/VI group (3.5%).

Quality of Life

Changes in HRQoL were assessed in the four parallel-group studies using the SGRQ total score. In addition, two of the tiotropium-controlled studies (DB211360 and DB2113374) assessed HRQoL using the EQ-5D instrument; however, no formal between-group statistical analyses were conducted on the EQ-5D. The minimal clinically important difference (MCID) on the SGRQ total score is 4 units. The crossover studies did not report HRQoL outcomes. In study DB2113373, treatment with UMEC/VI resulted in statistically significant and clinically meaningful improvements in HRQoL as measured by the SGRQ versus placebo (least squares [LS] mean difference [MD] –5.51 [95% confidence interval (CI), –7.88 to –3.13]; $P < 0.001$); however, there were no differences in SGRQ total score between UMEC/VI and its individual components. In one study (ZEP117115), UMEC/VI demonstrated statistically significantly greater improvements in SGRQ score compared with TIO (LS MD –2.10 [95% CI, –3.61 to –0.59]; $P = 0.006$). Treatment with UMEC/VI showed greater improvement in SGRQ score than TIO in another study (DB2113374) but the difference was not statistically significant (LS MD –0.17 [95% CI, –2.85 to 2.52]; $P = 0.904$). In a third study (DB2113360), tiotropium showed greater improvement in SGRQ score than

UMEC/VI with the difference not reaching the level of statistical significance (LS MD 0.75 [95% CI, –2.12 to 3.63]; *P* = 0.607). In all three studies, both UMEC/VI and TIO achieved within-group clinically meaningful improvements in SGRQ scores from baseline; however, the clinical significance of the between-treatment group differences with UMEC/VI and TIO are uncertain.

Spirometry

The trough FEV_1 at treatment day 169 (week 24) was the primary end point in all four parallel-group studies. The MCID for FEV_1 has been reported to range from 0.1 L to 0.14 L.[6-9] In study DB2113373, UMEC/VI demonstrated statistically significant improvements in trough FEV_1 at week 24 compared with placebo, UMEC, and VI. LS MDs for the comparisons were 0.167 L (95% CI, 0.128 to 0.207; *P* < 0.001), 0.052 L (95% CI, 0.017 to 0.087; *P* = 0.004), and 0.095 L (95% CI, 0.060 to 0.130; *P* < 0.001), respectively.

In two of the TIO-controlled studies (DB2113360 and ZEP117115), treatment with UMEC/VI resulted in statistically significant improvements in trough FEV_1 at week 24 compared with TIO, with LS MD of 0.090 L (95% CI, 0.039 to 0.141; P < 0.001) and 0.112 L (95% CI, 0.081 to 0.144; P < 0.001). The improvement in trough FEV_1 versus TIO appeared to be clinically meaningful in study ZEP117115 but was of uncertain clinical significance in DB2113360 based on the lower end of the MCID range. In study DB2113374, the difference in FEV_1 between UMEC/VI and TIO was numerically in favour of UMEC/VI at 24 weeks with a LS MD of 0.060 L (95% CI, 0.010 to 0.109). However, inference of statistical significance between the two treatments in study DB2113374 could not be made because comparisons failed an a priori set hierarchy test.

Change from baseline in trough FEV_1 was a co-primary outcome (with post-dose EET) in the crossover endurance studies. In one of these studies (DB2114417), UMEC/VI showed a clinically relevant improvement of 0.211 L in FEV_1 at 12 weeks compared with placebo. However, an inference of statistical significance between the two treatments could not be made as a higher order comparison between UMEC/VI 125 mcg/25 mcg and placebo in improvement in EET was not statistically significant. In the other exercise endurance study (DB2114418), treatment with UMEC/VI demonstrated statistically significant and clinically meaningful improvement in trough FEV_1 at week 12 compared with placebo (LS MD 0.243 L [95% CI, 0.202 to 0.284]; *P* < 0.001) and with VI (LS MD 0.132 L [95% CI, 0.081 to 0.183]; P < 0.001). UMEC/VI was also statistically significantly improved versus UMEC, but the clinical significance of the between-group difference is uncertain (LS MD 0.099 L [95% CI, 0.041 to 0.157]; P < 0.001).

Dyspnea

Dyspnea was assessed using the TDI. The MCID of the TDI has been reported as 1 unit. The TDI at week 24 scores were reported in three studies (DB2113373, DB2113360, and DB2113374). In DB2113373, all the treatment groups including placebo had improvements in TDI score from baseline with the difference between UMEC/VI and placebo being statistically significant and clinically meaningful in favour of UMEC/VI (LS MD 1.2 [95% CI, 0.7 to 1.7]; *P* < 0.001). The between-group LS MDs for UMEC/VI versus UMEC alone and UMEC/VI versus VI alone were 0.3 units (95% CI, –0.2 to 0.7) and 0.4 units (95% CI, –1.0 to 0.8), respectively. In studies DB2113360 and DB2113374, treatment with either UMEC/VI or TIO resulted in improvements in TDI scores from baseline with similar scores showing neither statistically significant nor clinically meaningful difference between the two (LS MD –0.1 units [95% CI, –0.7 to 0.5] in DB2113360, and 0.2 units [95% CI, –0.5 to 0.9] in DB2113374). Change in TDI score from baseline was not measured in study ZEP117117.

The crossover studies (DB2114417 and DB2114418) measured dyspnea on exercise using a 10-point modified Borg scale (MCID 1 unit). At the end of the studies, UMEC/VI demonstrated statistically

significant improvement versus placebo in study DB2114418 only; there was no evidence for a clinically meaningful improvement compared with any of the treatment groups. This could be because at baseline the patients in these studies were required to have less severe symptoms, which was necessary to ensure their safety during the exercise tests.

Exercise Tolerance

In one of the crossover studies (DB2114417), treatment with UMEC/VI resulted in modestly higher improvement in EET compared with placebo. The LS MD was 21.9 seconds (95% CI, –14.2 to 58.0; *P* = 0.234) was lower than the 45-second to 85-second MCID for EET.[10,11] Moreover, because of the predefined step-down closed testing procedure to adjust for multiplicity (a higher order comparison of UMEC/VI 125 mcg/25 mcg to placebo with respect to EET did not result in statistically significant difference), inference of statistical significance between UMEC/VI and placebo with regard to exercise endurance could not be made. In the other exercise endurance study (DB2114418), treatment with UMEC/VI demonstrated statistically significant and clinically meaningful improvement in EET compared with placebo. The LS MD was 69.4 seconds (s) (95% CI, 24.5 to 114.4; *P* = 0.003).

Other Comparisons

In the absence of head-to-head comparisons with other LABA/LAMA combination inhalers, the manufacturer provided an indirect comparison. Using the Bucher method, the manufacturer's analysis indicated no differences between UMEC/VI versus indacaterol plus tiotropium, indacaterol plus glycopyrronium, or fluticasone/salmeterol plus tiotropium with respect to change in trough FEV_1, HRQoL (assessed using SGRQ), rescue medication use, and dyspnea (assessed using TDI) at 12 week and 24 week time points. However, the findings from the indirect comparison should be interpreted with considerable caution given numerous important limitations of the analysis, largely related to poor reporting of methods used, the characteristics of the included studies, and the lack of comparisons related to key outcomes such as exacerbations, exercise tolerance, and adverse events.

Harms

Adverse Events

Incidence of overall adverse events (AEs) was generally similar across treatment groups in each study. AEs were reported in 51% of UMEC/VI, 48% of vilanterol, 52% of umeclidinium, and 46% of placebo patients in study DB2113373. In the TIO-controlled studies (DB2113374, DB2113360, and ZEP117115), the percentage of patients with AEs ranged from 44% to 59% for UMEC/VI and from 39% to 59% for TIO. In the crossover studies (DB2114417 and DB2114418), the percentage of AEs ranged from 23% to 44% for UMEC/VI, 29% to 36% for vilanterol, 12% to 30% for umeclidinium, and 27% to 39% for placebo patients. Nasopharyngitis and headache were the most common AEs in all the studies (range: 2% to 10% nasopharyngitis; 0 to 10% headaches).

Serious Adverse Events

The frequency of serious adverse events (SAEs) was generally low across all the studies. UMEC/VI SAEs were reported in 5% of UMEC/VI, 6% of vilanterol, 6% of umeclidinium, and 3% of placebo patients in study DB2113373. In the TIO-controlled studies (DB2113374, DB2113360, and ZEP117115), the percentage of patients with SAEs ranged from 3% to 10% for UMEC/VI and from 4% to 6% for TIO. In the crossover studies (DB2114417 and DB2114418), the percentage of SAEs ranged from 2% to 3% for UMEC/VI, 3% to 9% for vilanterol, 0% to 3% for umeclidinium, and 3% to 4% for placebo patients. COPD and related sequelae were reported most frequently as SAEs (range: < 1% to 3% across all studies) and invariably resulted in withdrawal from the study (see Withdrawals Due to Adverse Events).

Withdrawals Due to Adverse Events

The proportions of patients withdrawn due to AEs were similar across studies and did not exceed 10% in any one treatment group. In all the studies apart from those that tested exercise endurance, COPD was the most common AE leading to withdrawal. For the exercise endurance studies, dyspnea was the most common cause of withdrawals due to adverse events (WDAEs).

Notable Harms

Incidence of cardiovascular disorders, anticholinergic effects, and pneumonia, considered as notable harms in this review, were generally low in all studies. Pneumonia occurred in 3% or less of patients across studies. Dry mouth occurred in 1% or less of patients across studies. The highest proportion of cardiovascular AEs occurred in studies DB2113373 and DB2113360. In DB2113373, cardiovascular AEs were reported in 8% of UMEC/VI, 7% of vilanterol, 10% of umeclidinium, and 9% of placebo patients. In DB2113360, cardiovascular AEs were reported in 11% of UMEC/VI, 10% of vilanterol, and 4% of tiotropium patients. Despite nominally more cardiovascular AEs with UMEC/VI versus tiotropium in this study, the other two TIO-controlled studies did not report clear differences between these treatments.

Conclusions

Six DB RCTs met the inclusion criteria for this review, three of which compared UMEC/VI with its components administered as monotherapies, as well as placebo, and another three studies compared UMEC/VI with tiotropium monotherapy. Two studies were 12-week crossover studies designed to assess effects on exercise tolerance and trough FEV_1 at week 12 while the remaining studies were parallel designs assessing effects on change in trough FEV_1 at week 24. None of the studies was designed to evaluate the comparative treatment effects of UMEC/VI on mortality and morbidity (e.g., hospitalizations and exacerbations), which were key outcomes for the review and identified by patient groups as important to them.

A statistically significant improvement in HRQoL (on the SGRQ) with UMEC/VI was found in only one study versus tiotropium and one study versus placebo. Treatment with UMEC/VI resulted in statistically significant improvements in trough FEV_1 at week 24 versus placebo and active comparators in each of the studies. However, the clinical relevance of the effects of UMEC/VI versus its individual components and TIO is somewhat difficult to judge given that in most cases the change in trough FEV_1 from baseline for the active comparators met or exceeded the within-group MCID of 0.1 L, making it less likely to observe a clinically important difference between groups. Hence, the clinical importance of the incremental gain in FEV_1 improvement with the combination of UMEC/VI versus a single long-acting bronchodilator is difficult to determine. Improvements in dyspnea (TDI score assessed in three studies) were in favour of UMEC/VI versus placebo in one study, but not versus TIO in two studies. Furthermore, only one of the two exercise endurance studies demonstrated a statistically and clinically significant improvement in the co-primary efficacy end points of post-dose EET and trough FEV_1 at week 12 in favour of UMEC/VI compared with placebo.

The manufacturer provided an indirect comparison that suggested no difference with between UMEC/VI and other LABA/LAMA combinations with respect to change in trough FEV_1, HRQoL, rescue medication use, and dyspnea at 12-week and 24-week time points. However, the findings from the indirect comparison should be interpreted with considerable caution given numerous important limitations of the analysis, largely related to poor reporting of methods used, the characteristics of the included studies, lack of head-to-head comparisons, and the lack of comparisons related to key outcomes such as exacerbations, exercise tolerance, and AEs.

The most common AEs with UMEC/VI were nasopharyngitis and headache. No clear association with the occurrence of cardiovascular, anticholinergic, or pneumonia events could be determined because events occurred infrequently and the studies were only 12 weeks to 24 weeks in duration.

TABLE 1: SUMMARY OF RESULTS: UMECLIDINIUM/VILANTEROL VERSUS PLACEBO, UMECLIDINIUM, AND VILANTEROL MONOTHERAPY — INTENTION-TO-TREAT POPULATION

Outcome [a]	DB2113373			
	PLACEBO N = 280	UMEC N = 418	VI N = 421	UMEC/VI N = 413
***Deaths,* n (%)[b]**	0	1 (< 1)	3(< 1)	3 (< 1)
Health Care Resource Utilization,[c] n (%)				
Hospitalization	9 (3.2)	14 (3.3)	17 (4.0)	13 (3.1)
Emergency room visit	15 (5.4)	18 (2.9)	17 (4.0)	8 (1.9)
On-treatment Exacerbation,[d] n (%)				
Number of patients, n (%)	35 (12.5)	33 (7.9)	39 (9.3)	27 (6.5)
Withdrawn due to COPD exacerbation, n (%)	34 (12)	33 (7.9)	38 (9.0)	25 (6.1)
HRQoL: SGRQ Total Score				
LS mean (SE) day 168	46.62 (0.950)	41.93 (0.753)	41.43 (0.760)	41.11 (0.749)
LS mean change (SE) from baseline	–2.56 (0.950)	–7.25 (0.753)	–7.75 (0.760)	–8.07 (0.749)
LS MD (95% CI) (UMEC/VI vs. comparator	–5.51 (–7.88 to –3.13)	–0.82 (–2.90 to 1.27)	–0.32 (–2.41 to 1.78)	-
P value	< 0.001	0.441	0.767	-
Trough FEV_1 (Litres), Week 24				
LS mean (SE)	1.239 (0.0158)	1.354 (0.0126)	1.311 (0.0127)	1.406 (0.0126)
LS mean change (SE) from baseline	0.004 (0.0158)	0.119 (0.0126)	0.076 (0.0127)	0.171 (0.0126)
LS MD (95% CI) (UMEC/VI vs. comparator)	0.167 (0.128 to 0.207)	0.052 (0.017 to 0.087)	0.095 (0.060 to 0.130)	-
P value	< 0.001	0.004	< 0.001	
Dyspnea: TDI Focal Score				
LS Mean (SE) day 168	1.2 (0.20)	2.2 (0.16)	2.1 (0.16)	2.4 (0.16)
LS MD (95% CI) (UMEC/VI vs. comparator)	1.2 (0.7 to 1.7)	0.3 (–0.2 to 0.7)	0.4 (–0.1 to 0.8)	-
P value	< 0.001	0.244	0.117	-
OR (95% CI) (UMEC/VI vs. comparator)	2.0 (1.5 to 2.8)	1.2 (0.9 to 1.6)	1.4 (1.0 to 1.8)	-
P value	< 0.001	0.143	0.038	-
Rescue Salbutamol Use, Weeks 1 to 24				
LS mean (SE)	4.1 (0.20)	3.8 (0.16)	3.2 (0.16)	3.3 (0.16)
LS mean change (SE) from baseline	–1.4 (0.20)	–1.7 (0.16)	–2.4 (0.16)	–2.3 (0.16)
LS MD (95% CI) (UMEC/VI vs. comparator)	–0.8 (–1.3 to –0.3)	–0.6 (–1.0 to –0.1)	0.1 (–0.3 to 0.5)	-
P value	0.001	0.014	0.675	-

Outcome [a]	DB2113373			
	PLACEBO N = 280	UMEC N = 418	VI N = 421	UMEC/VI N = 413
AEs [e]				
On-treatment, n (%)	130 (46)	216 (52)	204 (48)	212 (51)
***SAEs* on-treatment, n (%)**	9 (3)	27 (6)	24 (6)	21 (5)
***WDAEs*, n (%)**	9 (3)	34 (8)	24 (6)	23 (6)
Notable harms [e]				
Cardiovascular, n (%)	26 (9)	41 (10)	31 (7)	33 (8)
Anticholinergic syndrome, n (%)	8 (3)	18 (4)	14 (3)	10 (2)
Pneumonia, n (%)	2 (< 1)	6 (1)	4 (< 1)	8 (2)

AEs = adverse events; ANCOVA = analysis of covariance; CDR = CADTH Common Drug Review; CI = confidence interval; COPD = chronic obstructive pulmonary disease; DB = double-blind; FEV_1 = forced expiratory volume in one second; HRQoL = health-related quality of life; LS = least squares; MD = mean difference; n = number of patients with event; N = number of patients; OR = odds ratio; *P* = probability; SAEs = serious adverse events; SE = standard error; SGRQ = St. George's Respiratory Questionnaire; TDI = Treatment Dyspnea Index; UMEC = umeclidinium; UMEC/VI = umeclidinium/vilanterol; VI = vilanterol; vs. = versus; WDAEs = withdrawals due to adverse event.
Note: ANCOVA model with covariates of treatment, baseline, smoking status, and centre group.
[a] Refer to Table 11 for baseline data on reported outcomes.
[b] For this review, mortality (death) is considered an efficacy outcome.
[c] In the study, the denominator to calculate the percentage of patients with emergency room and hospital admissions was based on the total patients with health care provider contact during treatment. CDR used the total number of patients in a treatment group as the denominator.
[d] In the study, percentages of patients withdrawing due to COPD exacerbation were calculated using the number of COPD exacerbations as the denominator. CDR used the total number of patients in a treatment group as the denominator.
[e] On-treatment AEs and SAEs were defined as those occurring with an onset on or after the date of the first dose of study drug, and up to one day after the date of the last recorded dose of study drug.
Source: Clinical Study Report for DB2113373.[9]

TABLE 2: SUMMARY OF RESULTS: UMECLIDINIUM/VILANTEROL VERSUS TIOTROPIUM — INTENTION-TO-TREAT POPULATION

Outcome[a]	DB2113360			DB2113374		ZEP117115	
	VI 25 mcg N = 205	UMEC/VI FDC N = 207	TIO 18 mcg N = 203	UMEC/VI FDC N = 217	TIO 18 mcg N = 215	UMEC/VI FDC N = 454	TIO 18 mcg N = 451
Deaths, n (%)[b]	1 (< 1)	1 (< 1)	0	1 (< 1)	2 (< 1)	2 (< 1)	5 (1)
Health Care Resource Utilization,[c] n (%)							
Hospitalization	9 (4.4)	1 (0.5)	3 (1.5)	11 (5.1)	6 (2.8)	2 (4.4)	5 (1)
Emergency room visit	7 (3.4)	5 (2.4)	5 (2.5)	10 (4.6)	6 (2.8)	2 (4.4)	4 (1.0)
On-treatment Exacerbation,[d] n (%)							
Number of patients	17 (8.3)	14 (6.8)	11 (5.4)	26 (12.0)	14 (6.5)	16 (3.5)	29 (6.4)
Withdrawn due to COPD exacerbation	16 (7.8)	13 (6.3)	10 (4.9)	24 (11)	12 (5.6)	16 (3.5)	29 (6.4)
HRQoL: SGRQ Total Score							
LS mean (SE) day 168	41.48 (1.058)	42.90 (1.017)	42.15 (1.054)	39.17 (0.981)	39.34 (0.954)	41.35 (0.538)	43.45 (0.548)
LS mean change (SE) from baseline, day 168	–8.29 (1.06)	–6.87 (1.02)	–7.62 (1.05)	–9.95 (0.98)	–9.78 (0.95)	–7.27 (0.538)	–5.17 (0.548)
LS MD (95% CI), (UMEC/VI vs. comparator)	1.42 (–1.46 to 4.30)	-	0.75 (–2.12 to 3.63)	-	–0.17 (–2.85 to 2.52)	-	–2.10 (–3.61 to –0.59)
P value	0.334	-	0.607	-	0.904	-	0.006
Trough FEV_1 (Litres), Week 24							
LS mean (SE)	1.431 (0.0189)	1.521 (0.0183)	1.431 (0.0186)	1.355 (0.0180)	1.295 (0.0176)	1.457 (0.0114)	1.345 (0.0115)
LS mean change (SE) from baseline at day 169	0.121 (0.019)	0.211 (0.018)	0.121 (0.019)	0.208 (0.018)	0.149 (0.018)	0.205 (0.0114)	0.093 (0.0115)
LS MD (95% CI), (UMEC/VI vs. comparator)	0.090 (0.039 to 0.142)	-	0.090 (0.039 to 0.141)	-	0.060 (0.010 to 0.109)	-	0.112 (0.081 to 0.144)
P value	< 0.001	-	< 0.001	-	0.0182	-	< 0.001
Dyspnea: TDI Focal Score							
LS mean (SE) day 168	2.1 (0.2)	2.3 (0.2)	2.4 (0.2)	2.3 (0.3)	2.1 (0.2)	NR	NR
LS MD (95% CI), (UMEC/VI vs. comparator)	0.2 (–0.4 to 0.8)	-	–0.1 (–0.7 to 0.5)	-	0.2 (–0.5 to 0.9)	NR	NR
P value	0.49	-	0.72	-	0.55	NR	NR

Outcome[a]	DB2113360			DB2113374		ZEP117115	
	VI 25 mcg N = 205	UMEC/VI FDC N = 207	TIO 18 mcg N = 203	UMEC/VI FDC N = 217	TIO 18 mcg N = 215	UMEC/VI FDC N = 454	TIO 18 mcg N = 451
Rescue Salbutamol Use, Week 1–24							
LS mean (SE)	2.8 (0.21)	2.5 (0.20)	3.2 (0.21)	2.9 (0.23)	3.5 (0.22)	[redacted]	[redacted]
LS mean change (SE) from baseline	–1.8 (0.2)	–2.0 (0.2)	–1.4 (0.2)	–2.7 (0.23)	–2.1 (0.22)	–1.3 (0.09)	–0.8 (0.09)
LS MD (95% CI), (UMEC/VI vs. comparator)	–0.3 (–0.8 to 0.3)	-	–0.7 (–1.2 to –0.1)	-	0.6 (–1.2 to 0.0)	-	–0.5 (–0.7 to –0.2)
P value	0.39	-	0.022	-	0.07	-	< 0.001
AEs[e]							
On-treatment, n (%)	99 (47)	108 (51)	82 (39)	127 (59)	126 (59)	202 (44)	190 (42)
***SAEs* on-treatment, n (%)**	15 (7)	7 (3)	13 (6)	22 (10)	9 (4)	16 (4)	17 (4)
WDAEs, n (%)	10 (5)	10 (5)	9 (4)	20 (9)	11 (5)	18 (4)	14 (3)
Notable Harms[e]							
Cardiovascular, n (%)	21 (10)	24 (11)	9 (4)	13 (6)	18 (8)	9 (2)	7 (2)
Anticholinergic syndrome, n (%)	5 (2)	7 (3)	6 (3)	8 (4)	9 (4)	NR	NR
Pneumonia, n (%)	3 (1)	0	7 (3)	18 (8)	10 (5)	1 (< 1)	3 (1)

AEs = adverse events; ANCOVA = analysis of covariance; CDR = CADTH Common Drug Review; CI = confidence interval; COPD = chronic obstructive pulmonary disease; DB = double-blind; FEV_1 = forced expiratory volume in one second; FDC = fixed-dose combination; HRQoL = health-related quality of life; LS = least squares; mcg = microgram; MD = mean difference; n = number of patients with event; N = number of patients; NR = not reported; OR = odds ratio; *P* = probability; SAE = serious adverse event; SE = standard error; SGRQ = St. George's Respiratory Questionnaire; SOBDA = shortness of breath with daily activities; TDI = Treatment Dyspnea Index; TIO = tiotropium; UMEC = umeclidinium; UMEC/VI = umeclidinium/vilanterol; VI = vilanterol; vs. = versus; WDAEs = withdrawals due to adverse event.
Note: ANCOVA model with covariates of treatment, baseline, smoking status, and centre group.
[a] Refer to Table 12 for baseline data on reported outcomes.
[b] For this review, mortality (death) is considered an efficacy outcome.
[c] In the study, the denominator to calculate the percentage of patients with emergency room and hospital admissions was based on the total patients with health care provider contact during treatment. CDR used the total number of patients in a treatment group as the denominator. For study ZEP117115, emergency room visits and hospital admissions were reported for on-treatment COPD exacerbations only.
[d] In the study, percentages of patients withdrawing due to COPD exacerbation were calculated using the number of COPD exacerbation as the denominator. CDR used the total number of patients in a treatment group as the denominator.[e] On-treatment AEs and SAEs were defined as those occurring with an onset on or after the date of the first dose of study drug, and up to one day after the date of the last recorded dose of study drug.
Source: Clinical Study Reports for DB2113360, DB2113374, and ZEP117115.[6,7,11]

TABLE 3: SUMMARY OF RESULTS: CROSSOVER STUDIES — INTENTION-TO-TREAT POPULATION

Outcome[a]	DB2114417				DB2114418			
	PLACEBO N = 170	UMEC N = 49	VI N = 76	UMEC/VI FDC N = 152	PLACEBO N = 151	UMEC N = 40	VI N = 64	UMEC/VI FDC N = 130
Deaths, n (%)[b]	0	0	0	0	0	0	0	1
Health Care Resource Utilization,[c] ***n (%)***								
Hospitalization	2 (1.2)	0	0	0	2 (1.3)	0	0	0
Emergency room visit	2 (1.2)	0	0	0	1 (< 1)	0	0	0
On-treatment Exacerbation,[d] ***n (%)***								
Number of patients	11 (6.5)	1 (2.0)	4 (5.3)	8 (5.3)	16 (10.6)	0	3 (4.7)	2 (1.5)
Withdrawn due to COPD exacerbation	10 (5.9)	0	4 (5.3)	8 (5.3)	14 (9.3)	0	2 (3.1)	2 (1.5)
Trough FEV_1 (Litres), Week 12								
LS mean (SE)	1.404 (0.0149)	1.491 (0.0264)	1.503 (0.0218)	1.615 (0.0156)	1.277 (0.0156)	1.421 (0.0267)	1.388 (0.0222)	1.520 (0.0156)
LS mean change (SE) from baseline	–0.032 (0.0149)	0.054 (0.0264)	0.067 (0.0218)	0.178 (0.0156)	–0.043 (0.0156)	0.101 (0.0267)	0.069 (0.0222)	0.200 (0.0156)
LS MD (95% CI), (UMEC/VI vs. comparator)	0.211 (0.172 to 0.249)	0.124 (0.067 to 0.181)	0.111 (0.062 to 0.161)	-	0.243 (0.202 to 0.284)	0.099 (0.041 to 0.157)	0.132 (0.081 to 0.183)	-
P value	< 0.001	< 0.001	< 0.001		< 0.001	< 0.001	< 0.001	-
Exercise Dyspnea Scale (Modified Borg Index), Week 12								
LS mean (SE)	3.67 (0.114)	3.51 (0.208)	4.06 (0.172)	3.62 (0.120)	3.31 (0.114)	2.99 (0.205)	2.94 (0.167)	2.95 (0.117)
LS mean change (SE) from baseline	–0.30 (0.114)	–0.45 (0.208)	0.09 (0.172)	–0.35 (0.120)	–0.01 (0.114)	–0.33 (0.205)	–0.37 (0.167)	–0.37 (0.117)
LS MD (95% CI) UMEC/VI vs. comparator	–0.05 (–0.37 to 0.27)	0.11 (–0.36 to 0.57)	–0.44 (–0.85 to –0.04)	-	–0.36 (–0.67 to –0.05)	–0.04 (–0.49 to 0.42)	0.00 (–0.39 to 0.40)	-
P value	0.758	0.656	0.032	-	0.025	0.870	0.982	-
3-hour Post-dose EET (Seconds) Week 12								
LS mean change (SE) from baseline	36.7 (13.17)	63.2 (23.93)	26.7 (19.72)	58.6 (13.82)	0.1 (16.66)	25.1 (30.18)	30.7 (24.79)	69.5 (17.09)
LS MD (95% CI), (UMEC/VI vs. comparator)	21.9 (-14.2 to 58.0)	–4.6 (–57.6 to 48.4)	31.9 (–14.1 to 77.9)	-	69.4 (24.5 to 114.4)	44.4 (–21.8 to 110.6)	38.8 (-18.9 to 96.5)	-

Outcome[a]	DB2114417				DB2114418			
	PLACEBO N = 170	UMEC N = 49	VI N = 76	UMEC/VI FDC N = 152	PLACEBO N = 151	UMEC N = 40	VI N = 64	UMEC/VI FDC N = 130
P value	0.234	0.865	0.174	-	0.003	0.188	0.187	-
Rescue Salbutamol Use, Week 1–24								
LS mean (SE)	2.4 (0.11)	2.2 (0.19)	2.1 (0.16)	1.8 (0.12)	3.0 (0.14)	2.3 (0.25)	2.3 (0.20)	1.8 (0.14)
LS mean change (SE) from baseline	–0.4 (0.11)	–0.6 (0.19)	–0.7 (0.16)	–1.0 (0.12)	–0.3 (0.14)	–1.0 (0.25)	–1.0 (0.20)	–1.4 (0.14)
LS MD (95% CI) (UMEC/VI vs. comparator	–0.6 (–0.8 to –0.3)	–0.4 (–0.7 to 0.0)	–0.2 (–0.6 to 0.1)	-	–1.2 (–1.5 to –0.8)	–0.4 (–1.0 to 0.1)	–0.4 (–0.9 to 0.0)	-
P value	< 0.001	0.074	0.162	-	< 0.001	0.099	0.068	-
AEs[e]								
On-treatment, n (%)	46 (27)	6 (12)	22 (29)	35 (23)	59 (39)	12 (30)	23 (36)	57 (44)
***SAEs* on-treatment, n (%)**	6 (4)	0	7 (9)	4 (3)	4 (3)	1 (3)	2 (3)	3 (2)
WDAEs total, n (%)	9 (5)	2 (4)	5 (7)	6 (4)	8 (5)	1 (3)	4 (6)	5 (4)
Notable Harms[e]								
Cardiovascular, n (%)	6 (4)	1 (2)	5 (7)	2 (1)	2 (1)	1 (3)	1 (2)	5 (4)
Anticholinergic syndrome, n (%)	2 (1)	0	2 (3)	0	6 (4)	0	1 (2)	5 (4)
Pneumonia, n (%)	1 (< 1)	1 (2)	1 (1)	0	2 (1)	0	1 (2)	1 (< 1)

AEs = adverse events; CDR = CADTH Common Drug Review; CI = confidence interval; COPD = chronic obstructive pulmonary disease; DB = double-blind; EET = exercise endurance time; FEV_1 = forced expiratory volume in one second; FDC = fixed-dose combination; LS = least squares; MD = mean difference; n = number of patients with event; N = number of patients; *P* = probability; SAEs = serious adverse events; SE = standard error; UMEC = umeclidinium; UMEC/VI = umeclidinium/vilanterol; VI = vilanterol; vs. = versus; WDAEs = withdrawals due to adverse event.

Note: ANCOVA model with covariates of treatment, baseline, smoking status, and centre group.

[a] Refer to Table 13 for baseline data on reported outcomes.

[b] For this review, mortality (death) is considered an efficacy outcome.

[c] In the studies, only health care resource utilization upon on-treatment COPD exacerbation was reported. CDR used the total number of patients in a treatment group as the denominator to calculate percentages.

[d] In these studies, COPD exacerbations were considered under lack of efficacy, not adverse events.

[e] On-treatment AEs and SAEs were defined as those occurring with an onset on or after the date of the first dose of study drug, and up to one day after the date of the last recorded dose of study drug.

Source: Clinical Study Reports for DB2114417 and DB2114418.[8,10]

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.[1] The term "COPD" is an umbrella for a spectrum of pulmonary processes involving a combination of airway inflammation (chronic bronchitis) and parenchymal destruction (emphysema).[3,12] There is overlap of COPD subtypes, with many individuals presenting with features of both chronic bronchitis and emphysema, as well as asthma, which differs fundamentally from COPD. Cigarette smoking dominates risk factors for COPD and is reported to be the principal underlying cause accounting for 80% to 90% of COPD cases.[3,12] Although disease activity and the nature of symptomatic impairment may vary from patient to patient, cough, excess sputum production, and dyspnea are the typical symptoms of COPD.[3]

COPD is a major public health problem and a leading cause of morbidity and mortality worldwide, comprising an economic and social burden that is both substantial and increasing. According to a 2009 Statistics Canada report, COPD affects 4% of the Canadian population ≥ 35 years of age.[4] Among COPD patients in Canada aged 35 years to 79 years, 7% had Stage II (moderate) or higher COPD.[13] Airflow limitation is determined by spirometry measurements such as forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC). A post-bronchodilator FEV_1/FVC ratio < 0.70 indicates airway obstruction.[1] The Canadian Thoracic Society (CTS) classification of COPD severity and lung function is summarized in Table 4. The CTS classification of COPD closely resembles the Global Initiative for Obstructive Lung Disease (GOLD) staging classification used in the studies.

TABLE 4: CANADIAN THORACIC SOCIETY CLASSIFICATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE SEVERITY BY SYMPTOMS, DISABILITIES, AND IMPAIRMENT OF LUNG FUNCTION

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

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; m = metre; NR = not reported.
Source: O'Donnell et al., Canadian Thoracic Society COPD Recommendations — 2008 Primary Care Updates.[2]

Recent statistics on hospital admissions show that COPD accounts for the highest rate of hospital admission among major chronic illnesses in Canada, exceeding hospital admission rates of heart attacks.[14] Hospital admissions for COPD exacerbations in Canada averaged a 10-day length of stay at a cost of $10,000 per stay in 2008, and an estimated total cost of hospitalizations of $1.5 billion per year.[14] The readmission rate for COPD (18% readmitted once and 14% readmitted twice within a year) was also

higher than other chronic illnesses.[14] COPD is the only chronic disease in which mortality is still increasing.[14]

1.2 Standards of Therapy

Both pharmacologic and non-pharmacologic interventions are key to the management of COPD patients with the aim to control symptoms, decrease exacerbations, and improve patient function and quality of life.[15] Quitting cigarette smoking is the key modifiable risk factor for COPD, and the single most effective intervention for improved lung function, reduced chronic cough and airways mucus production, and decreased mortality from COPD.[12,15]

Pharmacotherapy for COPD follows a stepwise approach driven by disease severity (i.e., symptoms or disability and spirometry) and the frequency of acute exacerbations. Inhaled bronchodilators are the mainstays of drug therapy for COPD. They are available as short- and long-acting beta2-agonists (SABA and LABA) and anticholinergic (short-acting muscarinic antagonist [SAMA] and long-acting muscarinic antagonist [LAMA]) drugs, as well as combinations of fixed-dose LABAs and inhaled corticosteroids (LABA plus ICS).[15] Antimuscarinic and beta2-agonist drugs are often used in combination for maximal improvement in dyspnea and function. Inhaled steroids may not be useful for mild disease; however, they may have more of a role in the management of moderate to severe COPD in patients with a history of exacerbations, when combined with a LABA.[15]

Phosphodiesterase inhibitors (theophylline, and more recently, roflumilast) are adjunctive therapies for COPD management that may be more effective in those with demonstrable neutrophilic airway inflammation.

Inhaled medications are most commonly delivered as pressurized metered-dose inhalers and dry powder inhalers (DPIs).

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.[2]

1.3 Drug

Umeclidinium bromide ("umeclidinium") plus vilanterol trifenatate ("vilanterol") (Anoro Ellipta) is a long-acting muscarinic antagonist/beta2-agonist (LAMA/LABA) fixed-dose combination (FDC) formulation with a Health Canada indication for 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 drug is available as dry powder for oral inhalation using an Ellipta device. Following oral inhalation, both of the two active ingredients act locally, targeting different receptors and pathways to produce bronchodilation. A combination of the competitive inhibitory effects on muscarinic M3 cholinergic receptors by umeclidinium and the stimulatory action of vilanterol on beta-2 adrenergic receptors results in dual bronchodilatory effect in the airways, which is maintained for 24 hours. The recommended dose is umeclidinium plus vilanterol 62.5 mcg/25 mcg once daily.

Indication under review
Indicated for long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema.
Listing criteria requested by sponsor
List in a similar manner to tiotropium, as a maintenance bronchodilator treatment for COPD.

TABLE 5: KEY CHARACTERISTICS OF UMECLIDINIUM PLUS VILANTEROL AND GLYCOPYRRONIUM PLUS INDACATEROL

	Umeclidinium + Vilanterol	Glycopyrronium + Indacaterol
Mechanism of Action	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 once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD including chronic bronchitis and emphysema
Route of Administration	Inhalation Fixed-dose combination, Ellipta device	Inhalation Fixed-dose combination, Breezhaler device
Recommended Dose	Umeclidinium + vilanterol 62.5 mcg/25 mcg once daily	Indacaterol + glycopyrronium 110 mcg/50 mcg once daily
Serious Side Effects/ 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
Other	Dry powder inhaler	Dry powder inhaler

COPD = chronic obstructive pulmonary disease; M3 = muscarinic M3 cholinergic receptors; mcg = microgram.
[a] Health Canada indication.
Source: Product monographs — Anoro Ellipta[16] and Ultibro Breezhaler.[17]

2. OBJECTIVES AND METHODS

2.1 Objectives

To evaluate the beneficial and harmful effects of umeclidinium/vilanterol (Anoro Ellipta) for the long-term bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema.

2.2 Methods

Studies selected for inclusion in this review were the pivotal studies provided in the manufacturer's submission to the CADTH Common Drug Review (CDR) as well as those meeting the selection criteria presented in Table 6.

TABLE 6: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Patients diagnosed with COPD, including chronic bronchitis and emphysema **Subgroups:** Age, sex, BMI, COPD severity, chronic bronchitis, emphysema, smoking status, bronchodilator reversibility, concomitant COPD medication use, indicators of asthma
Intervention	Umeclidinium bromide and vilanterol trifenatate (Anoro Ellipta) 62.5 mcg/25 mcg once daily
Comparators	The following comparators used alone or in combination (as appropriate): LABA (e.g., salmeterol, formoterol, indacaterol, vilanterol) SABA (e.g., salbutamol) LAMA (e.g., tiotropium, glycopyrronium, aclidinium) SAMA (e.g., ipratropium) ICS (e.g., fluticasone propionate, fluticasone furoate, budesonide) Roflumilast Theophylline Placebo
Outcomes	**Key efficacy outcomes:** • Mortality (all-cause) • Mortality due to COPD • Health care resource utilization (e.g., hospitalization, emergency room visits) • Exacerbations, and time to first exacerbation • Quality of life • Spirometry (e.g., FEV_1, expiratory capacity) • Symptoms (including dyspnea) • 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: cardiovascular-related, pneumonia, anticholinergic
Study Design	Published and unpublished RCTs

AEs = adverse events; BMI = body mass index; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second; ICS = inhaled corticosteroids; LABA = long-acting beta2-agonist; LAMA = long-acting muscarinic antagonist; mcg = microgram; RCTs = randomized controlled trials; SABA = short-acting beta2-agonist; SAEs = serious adverse events; SAMA = short-acting muscarinic antagonist; WDAEs = withdrawals 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 through Ovid; Embase (1974–) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Patient Headings), and keywords. The main search concepts were Anoro Ellipta (umeclidinium/vilanterol).

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.

The initial search was completed on August 26, 2014. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on December 10, 2014. Regular search updates were performed on databases that do not provide alert services.

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

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 7, Table 8, and Table 9.

3. RESULTS

3.1 Findings From the Literature

A total of 12 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 7, Table 8, and Table 9 and described in Section 3.2. There were no excluded studies.

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

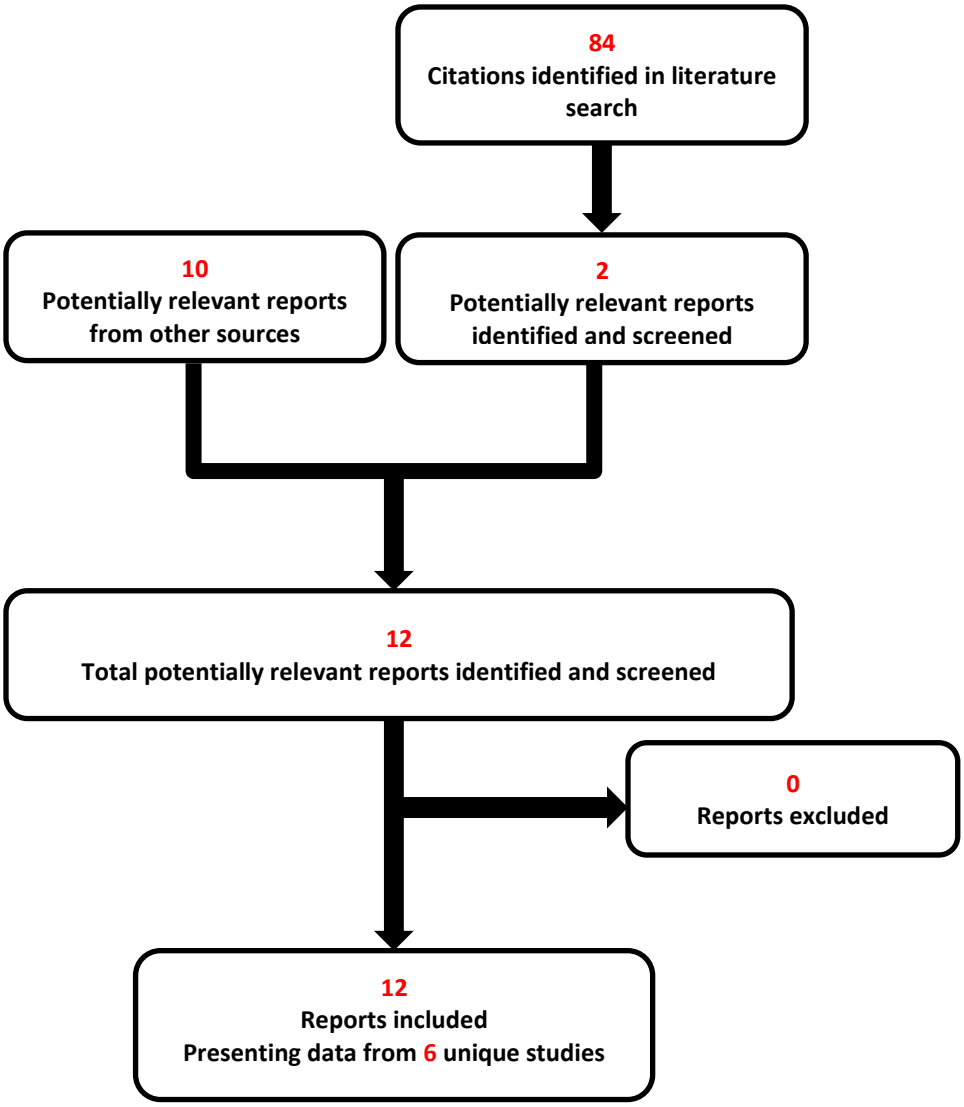

TABLE 7: DETAILS OF INCLUDED STUDIES: UMECLIDINIUM/VILANTEROL VERSUS PLACEBO, UMECLIDINIUM, AND VILANTEROL MONOTHERAPY

		DB2113373
DESIGNS & POPULATIONS	**Study Design**	Double-blind, placebo-controlled, parallel-group, randomized controlled trial
	Locations	163 centres in 13 countries: Bulgaria, Canada, Chile, Czech Republic, Greece, Japan, Mexico, Poland, Russia, South Africa, Spain, United States, and Thailand
	Study Period	March 30, 2011 to April 5, 2012
	Randomized (N)	N = 1,536
	Inclusion Criteria	• Adult patients aged 40 years or older • Cigarette smoking history (≥ 10 pack-years) • Established COPD with airflow limitation that is not fully reversible • Post-salbutamol FEV_1 of ≤ 70% of predicted normal values • Post-salbutamol (FEV_1/FVC) ratio of < 0.7, and mMRC dyspnea scale score of ≥ 2
	Exclusion Criteria	• A current diagnosis of asthma or other respiratory disease • Hospitalization for COPD or pneumonia within 12 weeks prior to screening • Any clinically significant[a] uncontrolled disease at screening, including but not limited to historical or current evidence of clinically significant cardiovascular or endocrine disorder • Previous use of UMEC, VI, UMEC/VI, or FF/VI
DRUGS	**Intervention**	UMEC/VI 62.5 mcg/25 mcg administered once daily as oral inhalation through the NDPI device called Ellipta DPI
	Comparator(s)	UMEC 62.5 mcg, VI 25 mcg, or placebo delivered once daily in identical manner as intervention
DURATION	**Phase**	
	Run-in	7 days to 10 days
	Double-blind	24 weeks
	Follow-up	7 days after the end of study treatment
OUTCOMES	**Primary End Point**	Trough FEV_1 on day 169 (week 24)
	Other End Points	TDI focal score at day 168, weighted mean FEV_1 0 to 6 hours post-dose on day 168, SGRQ total score on day 168
NOTES	**Publications**	Donohue et al., 2013[18]

COPD = chronic obstructive pulmonary disease; DB = double-blind; DPI = dry powder inhaler; FEV_1 = forced expiratory volume in one second; FF/VI = fluticasone furoate plus vilanterol combination; FVC = forced vital capacity; mcg = microgram; mMRC = modified Medical Research Council; N = number of patients; NDPI = Novel Dry Powder Inhaler; SGRQ = St. George's Respiratory Questionnaire; TDI = Treatment Dyspnea Index; UMEC = umeclidinium; UMEC/VI = umeclidinium/vilanterol; VI = vilanterol.

[a] Significant was defined as any disease that, in the opinion of the investigator, would put the safety of the patient at risk through disease or condition exacerbation during the study.

Source: Clinical Study Report for DB2113373.[9]

TABLE 8: DETAILS OF INCLUDED STUDIES: UMECLIDINIUM/VILANTEROL VERSUS TIOTROPIUM MONOTHERAPY

		DB2113360	DB2113374	ZEP117115
DESIGNS & POPULATIONS	**Study Design**	DB, double-dummy, parallel-group, RCT		
	Locations	91 centres in 9 countries: Germany, Italy, Mexico, Peru, Poland, Romania, Russia, Ukraine, and US	95 centres in 10 countries: Argentina, Australia, Canada, Chile, Germany, Mexico, Romania, South Africa, South Korea, and US	71 centres in 8 countries: Bulgaria, Canada, Germany, Hungary, Romania, Russia, Spain, and US
	Randomized (N)	N = 846	N = 872	N = 905
	Study Period	March 21, 2011 to April 24, 2012	March 21, 2011 to April 10, 2012	January 23, 2013 to October 1, 2013
	Inclusion Criteria	• Adult patients aged 40 years or older • Cigarette smoking history ≥ 10 pack-years • Established COPD with airflow limitation that is not fully reversible • Post-salbutamol FEV_1 of ≤ 70% of predicted normal values • Post-salbutamol (FEV_1/FVC) ratio of < 0.7, and mMRC dyspnea scale score of ≥ 2		
	Exclusion Criteria	• Women who were pregnant or lactating or were planning on becoming pregnant during the study • Hospital admission for COPD or pneumonia within 12 weeks before screening • A current diagnosis of asthma or other respiratory disease • Hospitalization for COPD or pneumonia within 12 weeks prior to screening • Any clinically significant[b] uncontrolled disease at screening including but not limited to historical or current evidence of clinically significant cardiovascular or endocrine disorder • Previous use of UMEC, VI, UMEC/VI, or FF/VI		
DRUGS	**Intervention**[a]	UMEC/VI 62.5 mcg/25 mcg administered once daily as oral inhalation through the NDPI device called Ellipta DPI		
	Comparator(s)[a]	TIO 18 mcg, administered once daily as oral inhalation through the HandiHaler VI 25 mcg, administered once daily as oral inhalation through Ellipta DPI	TIO 18 mcg administered once daily as oral inhalation through the HandiHaler	TIO 18 mcg administered once-daily as oral inhalation through the HandiHaler

		DB2113360	DB2113374	ZEP117115
DURATION	**Phase**			
	Run-in	7 days to 10 days		
	Double-blind	24 weeks		
	Follow-up	7 days after the end of study treatment or early withdrawal		
OUTCOMES	**Primary End Point**	Trough FEV_1 on treatment day 169, defined as the mean of the FEV_1 values obtained at 23 hours and 24 hours after dosing on day 168 (i.e., at week 24)		
	Other End Points	TDI focal score at treatment day 168 Weighted mean FEV_1 0 to 6 hours post-dose on day 168 HRQoL (SGRQ total score, EQ-5D) Health care resource use		Weighted mean FEV_1 0 to 6 hours post-dose on treatment day 168 and at other time points Rescue salbutamol use Time to onset and proportion of patients achieving an increase in FEV_1 of ≥ 12% and ≥ 200 mL above baseline at any time during 0 to 6 hours post-dose on treatment day 1
NOTES	**Publications**	Decramer et al., 2014 [19]		Maleki-Yazdi et al., 2014[20]

COPD = chronic obstructive pulmonary disease; DB = double-blind; EQ-5D = EuroQol 5-Dimensions Questionnaire; FEV_1 = forced expiratory volume in one second; FF/VI = fluticasone furoate plus vilanterol combination; FVC = forced vital capacity; HRQoL = health-related quality of life; mcg = microgram; mL = millilitre; mMRC = modified Medical Research Council; N = number of patients; NDPI = Novel Dry Powder Inhaler; RCT = randomized controlled trial; SGRQ = St. George's Respiratory Questionnaire; TDI = Treatment Dyspnea Index; TIO = tiotropium; UMEC = umeclidinium; UMEC/VI = umeclidinium/vilanterol; VI = vilanterol.

[a] Although UMEC/VI 125 mcg/25 mcg (as well as UMEC 125 mcg) was also tested, interventions and comparator data or information in this table focus only on UMEC/VI 62.5 mcg/25 mcg, which has a Health Canada indication for COPD and its individual components.

[b] Significant was defined as any disease that, in the opinion of the investigator, would put the safety of the patient at risk through disease or condition exacerbated during the study.

Source: Clinical Study Reports for DB2113360, DB2113374, and ZEP117115.[6,7,11]

TABLE 9: DETAILS OF INCLUDED STUDIES: CROSSOVER STUDIES

		DB2114417	DB2114418
DESIGNS & POPULATIONS	**Study Design**	DB, PC, RCT (crossover study)	
	Locations	31 centres in 6 countries: Bulgaria, Estonia, Germany, Russia, United Kingdom, and US	42 centres in 7 countries: Canada, Czech Republic, Denmark, South Africa, United Kingdom, Ukraine, and US
	Randomized (N)	N = 349	N = 308
	Study Period	March 16, 2011 to June 14, 2012	March 16, 2011 to July 16, 2012
	Inclusion Criteria	• Adult patients aged 40 years or older • Current or former cigarette smokers with ≥ 10 pack-years smoking history • Established COPD with airflow limitation that is not fully reversible • Post-salbutamol FEV_1 of ≥ 35% and ≤ 70% of predicted normal values • A resting FRC of ≥ 120% of predicted normal FRC at screening • Post-salbutamol (FEV_1/FVC) ratio of < 0.7, and mMRC dyspnea scale score of ≥ 2	
	Exclusion Criteria	• Pregnant or lactating women and those planning on becoming pregnant during the study • Hospital admission for COPD or pneumonia within 12 weeks before screening • A current diagnosis of asthma or other respiratory disease • Any clinically significant[b] uncontrolled disease at screening including, but not limited to, historical or current evidence of clinically significant cardiovascular or endocrine disorder Patients with lung volume reduction surgery within 12 months prior to screening	
DRUGS	**Intervention**[a]	UMEC/VI 62.5 mcg/25 mcg administered once daily as oral inhalation	
	Comparator(s)[a]	Placebo, UMEC 62.5 mcg, or VI 25 mcg, delivered once daily as monotherapy	
DURATION	**Phase**		
	Run-in	12 days to 21 days	
	Double-blind	Two 12-week periods separated by a 14-day washout period before crossing over	
	Follow-up	7 days after the end of the second treatment period or early withdrawal	
OUTCOMES	**Primary End Point**	The co-primary end points were: • EET post-dose at week 12, defined as the EET obtained 3 hours after dosing at week 12; and • Pre-bronchodilator and pre-dose FEV_1 at week 12 (treatment day 85), defined as the FEV_1 value obtained 24 hours after dosing on treatment day 84	

		DB2114417	DB2114418
	Other End Points	• Measures of lung volume • FEV_1 at week 12 measured three hours post-dose • Exercise dyspnea scale at week 12 • Rescue salbutamol use	
NOTES	**Publications**	None	

COPD = chronic obstructive pulmonary disease; DB = double-blind; EET = exercise endurance time; FEV_1 = forced expiratory volume in one second; FRC = functional residual capacity; FVC = forced vital capacity; mMRC = modified Medical Research Council; N = number of patients; PC = placebo-controlled; RCT = randomized controlled trial; UMEC = umeclidinium; VI = vilanterol.

[a] Although UMEC/VI 125 mcg/25 mcg (as well as UMEC 125 mcg) was also tested, interventions and comparator data or information in this table focus only on UMEC/VI (62.5 mcg/25 mcg), which has a Health Canada indication for COPD and its individual components.

[b] Significant was defined as any disease that, in the opinion of the investigator, would put the safety of the patient at risk through disease or condition exacerbated during the study.

Source: Clinical Study Reports for DB2114417 and DB2114418.[8,10]

3.2 Included Studies

3.2.1 Description of Studies

Six clinical trials provided in the manufacturer's submission to CDR met the inclusion criteria for this review. They were all phase 3 multi-centre, double-blind (DB), randomized controlled trials (RCTs) in which umeclidinium/vilanterol (UMEC/VI) 62.5 mcg/25 mcg fixed-dose combination (FDC) oral inhaler formulation was the intervention of primary interest for this review. Investigators or treating physicians could unblind a patient's treatment in case of an emergency. In that case, the patient was to be discontinued from the study, without revealing the patient's treatment assignment. Data for unblinded patients were handled similarly to partial deviation from protocol as described under the Statistical Analysis section. Details of activities undertaken during the run-in period were not provided for any of the studies. In one placebo-controlled study (DB2113373), patients were to be randomized in a 3:3:3:2 (3 active: 2 placebo) ratio. In all the tiotropium (TIO)–controlled studies (DB2113360, DB2113374, and ZEP117115), eligible patients were assigned to study treatment regimens in equal proportion. It was not reported in any of the clinical study reports of the studies included in this review that randomization was stratified by any parameter. The studies were all superiority studies. Other treatment groups included the following, depending on the study: UMEC/VI 125 mcg/25 mcg, UMEC 125 mcg, placebo, UMEC 62.5 mcg, VI 25 mcg, and TIO 18 mcg as once-daily monotherapy. Although included as treatment groups in two studies (DB2114417 and DB2114418), data and discussion in this review do not include the UMEC/VI (125 mcg/25 mcg) as a fixed-dose combination and UMEC 125 mcg, because neither of them has Health Canada approval for COPD. In all the studies, participants who were using inhaled corticosteroids (ICS) at least 30 days prior to screening were allowed to continue at a stable dose throughout the duration of the treatment period. The use of a consistent dose of ICS was permitted, provided the dose did not exceed 1,000 mcg of fluticasone propionate or equivalent, and ICS use was not to be initiated or discontinued within 30 days prior to screening.

One trial, DB2113373, evaluated the safety and efficacy of UMEC/VI, UMEC 62.5 mcg, VI 25 mcg, and placebo administered once daily, over a 24-week period (Table 7). All treatments were administered once daily in the morning by inhalation using the Ellipta Dry Powder Inhaler (DPI). In three other studies (DB2113360, DB2113374, and ZEP117115), UMEC 62.5 mcg/25 mcg once daily was compared with TIO 18 mcg once daily over a 24-week trial period (Table 8). In the DB2113360 trial, VI 25 mcg was one of the treatment groups. TIO was administered through HandiHaler, while all the other treatments were administered using the Ellipta DPI, although all the studies had double-dummy designs. Two other studies, DB2114417 and DB2114418, were placebo-controlled, combination and component, crossover study trials that evaluated the effect of UMEC/VI mcg, compared with UMEC 62.5 mcg, VI 25 mcg, and placebo on exercise endurance time (EET) and trough FEV1 (Table 9). Each study had two 12-week treatment periods that were separated by a 14-day washout period and all treatments were administered through the Ellipta DPI device. In both studies (DB2114417 and DB2114418), patients were randomized according to the treatment sequence in Table 10. Patients were randomized to receive a sequence consisting of two of the following treatments: UMEC/VI 125 mcg/25 mcg, UMEC/VI 62.5 mcg/25 mcg, UMEC 125 mcg, UMEC 62.5 mcg, VI 25 mcg, or placebo once daily.

TABLE 10: TREATMENT SEQUENCES FOR CROSSOVER STUDIES DB2114417 AND DB2114418

Sequence	Period 1	Period 2
1	UMEC/VI 125/25	UMEC/VI 62.5/25
2	UMEC/VI 125/25	UMEC/VI 62.5/25
3	UMEC/VI 125/25	UMEC 125
4	UMEC/VI 125/25	VI 25
5	UMEC/VI 125/25	Placebo
6	UMEC/VI 125/25	Placebo
7	UMEC/VI 62.5/25	UMEC 62.5
8	UMEC/VI 62.5/25	VI 25
9	UMEC/VI 62.5/25	Placebo
10	UMEC/VI 62.5/25	Placebo
11	UMEC 125	Placebo
12	UMEC 62.5	Placebo
13	VI 25	Placebo
14	UMEC/VI 62.5/25	UMEC/VI 125/25
15	UMEC/VI 62.5/25	UMEC/VI 125/25
16	UMEC 125	UMEC/VI 125/25
17	VI 25	UMEC/VI 125/25
18	Placebo	UMEC/VI 125/25
19	Placebo	UMEC/VI 125/25
20	UMEC 62.5	UMEC/VI 62.5/25
21	VI 25	UMEC/VI 62.5/25
22	Placebo	UMEC/VI 62.5/25
23	Placebo	UMEC/VI 62.5/25
24	Placebo	UMEC 125
25	Placebo	UMEC 62.5
26	Placebo	VI 25

UMEC = umeclidinium; UMEC/VI = umeclidinium/vilanterol; VI = vilanterol.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

The inclusion criteria were similar for all the trials. Patients were included if they were 40 years of age or older with a clinical history of COPD, a current or prior history of at least 10 pack-years of cigarette smoking, airflow limitation (defined by a measured post-salbutamol FEV_1/FVC ratio of < 0.70), post-salbutamol FEV_1 of ≤ 70% of predicted normal values, and a modified Medical Research Council (mMRC) score ≥ 2 (moderate to very severe symptoms) to demonstrate symptom burden (see Table 7, Table 8, and Table 9). Notable differences in inclusion criteria occurred in two crossover studies (DB2114417 and DB2114418), which investigated the comparative effect of UMEC/VI on exercise tolerance. In these studies, the patients were required to have a post-salbutamol FEV_1 of ≥ 35% and ≤ 70% predicted, and functional residual capacity (FRC) of ≥ 120% predicted was an additional requirement for inclusion (Table 9). These requirements were necessary because according to the investigators, it may be unsafe to involve patients with very severe COPD in exercise studies. The clinical expert involved in the review agreed with this concern.

Exclusion criteria for the studies were also similar and included respiratory conditions such as a current history of asthma as well as clinically significant medical conditions as determined by the investigator. Unlike the four parallel-group studies (DB2113373, DB2113374, DB2113360, and ZEP117115), previous use of UMEC/VI, UMEC, VI, or fluticasone furoate plus vilanterol combination (FF/VI) was not an exclusion criterion in studies DB2114417 or DB2114417 (Table 9). While patients with a history of COPD in the 12 months prior to screening were not generally excluded, those who had a COPD exacerbation at screening or a history of hospitalization for COPD or pneumonia within 12 weeks prior to screening were excluded.

b) Baseline Characteristics

Treatment groups within the studies were similar with regard to age, gender, and race. The mean age of patients in the included studies ranged from 61.6 years to 64.6 years. Although the majority of participants was male for all the studies (range: 55% to 71%, Table 11 and Table 12) differences in the representation of males and females in studies DB2114417 and DB2114478 were smaller (55% and 56% male, respectively, Table 13). In all the trials, the study populations were predominantly Caucasian (range: 76% to 98%). Smoking history was also similar between treatment groups for each study, although the proportion of current and former smokers varied across studies. In two studies (DB2113373 and DB2113360), the population was evenly split between current and former smokers (Table 11 and Table 12). One study (DB2113374) had a smaller total percentage of current smokers (45%) compared with 55% of former smokers, while the remaining studies (ZEP117115, DB2114417, and DB2114418) had more current smokers (57%, 63%, and 61%, respectively) than former smokers. This is reflected in the individual groups of the studies as indicated in Table 12 and Table 13. The mean smoking pack-years were similar among treatment groups and among studies and ranged from 41.6 to 54.0 across studies (Table 11, Table 12, and Table 13). The mean post-salbutamol per cent predicted FEV_1 at baseline was similar (range: 46.2% to 51.3%) across studies and treatment groups, with patients in the studies investigating exercise tolerance (DB2114417 and DB2114418) having the highest scores (51.3% for each study, Table 13). The mean post-bronchodilator reversibility across studies ranged from 10% to 16%. Disease severity as measured by GOLD Stage classifications was similar across studies and across treatment groups, with the majority of patients classified as Stages II and III. There were no patients with Stage I classification in any of the studies except one (DB2114418), which had two patients with disease designation of GOLD Stage I (Table 13). Study DB2114418 differed from the other exercise tolerance study (DB2114417) in that it included a patient with COPD classified as Stage IV (Table 13). For the four parallel-group studies, the majority of patients reported no COPD exacerbations requiring oral or systemic corticosteroids and/or antibiotics in the 12 months prior to screening. The proportions were similar across treatment groups and ranged from 65% to 72% in studies DB 2113373, DB2113360, and DB2113374 (Table 11 and Table 12), with 85% versus 82% for the UMEC/VI and TIO groups, respectively, in study ZEP117115 (Table 12). In the crossover studies DB2114417 and DB2114418, the proportions of patients who did not report COPD exacerbations requiring oral or systemic corticosteroids and/or antibiotics were 82% and 72%, respectively. Furthermore, the majority (81% to 96%) of patients in all the included studies did not have a COPD exacerbation resulting in hospitalization in the 12 months prior to screening, and the proportions were similar across treatment groups in each study. The use of ICS at baseline was generally similar across studies and between treatment groups for each study (Table 11, Table 12, and Table 13). Of note, 28% and 39% of patients reported receiving ICS at baseline in the crossover studies, DB2114417 and DB2114418, respectively.

TABLE 11: SUMMARY OF BASELINE CHARACTERISTICS: UMECLIDINIUM/VILANTEROL VERSUS PLACEBO, UMECLIDINIUM, AND VILANTEROL MONOTHERAPY

	DB2113373			
	PLACEBO N = 280	**UMEC N = 418**	**VI N = 421**	**UMEC/VI FDC N = 413**
Age years, mean (SD)	62.2 (9.04)	64.0 (9.16)	62.7 (8.52)	63.1 (8.71)
Range	(40, 83)	(40, 93)	(40, 88)	(40, 86)
Male gender, n (%)	195 (70)	298 (71)	285 (68)	305 (74)
Caucasian	237 (85)	354 (85)	364 (86)	348 (84)
Smoking History				
Current smoker	150 (54)	207 (50)	199 (47)	203 (49)
Pack-years, mean (SD)	47.2 (27.21)	46.8 (27.03)	44.7 (23.16)	46.5 (25.80)
Spirometry Measures				
Pre-bronchodilator FEV_1 (L), mean (SD)	1.198 (0.4470)	1.211 (0.4764)	1.237 (0.4861)	1.276 (0.5246)
Post-SALB FEV_1 (L), mean (SD)	1.355 (0.4629)	1.347 (0.4730)	1.402 (0.5011)	1.425 (0.5426)
Pre-bronchodilator FEV_1/FVC, mean (SD)	45.847 (11.2226)	46.202 (10.9409)	46.581 (11.4174)	47.329 (11.5136)
Post-SALB FEV_1/FVC, mean (SD)	47.082 (11.4695)	46.775 (11.0696)	47.372 (11.4928)	48.011 (11.4189)
Post-SALB per cent predicted FEV_1 (%), mean (SD)	46.7 (12.71)	46.8 (13.39)	48.2 (13.27)	47.8 (13.19)
Per cent reversibility to SALB (%), mean (SD)	15.3 (15.54)	13.9 (14.92)	15.7 (15.57)	13.9 (15.06)
Reversibility to SALB (mL), mean (SD)	158.5 (166.43)	137.3 (147.36)	164.4 (165.61)	151.2 (168.81)
COPD Severity (GOLD Stage), N (%)				
Stage II	119 (43)	191 (46)	197 (47)	201 (49)
Stage III	133 (48)	172 (41)	179 (43)	166 (40)
Stage IV	28 (10)	54 (13)	44 (10)	45 (11)
Reversible to SALB[a] patients, n (%)	91 (33)	121 (29)	155 (37)	129 (31)
ICS users, n (%)	137 (49)	219 (52)	212 (50)	212 (51)
mMRC dyspnea score, mean (SD)	2.4 (0.57)	2.4 (0.56)	2.4 (0.54)	2.4 (0.56)
Distribution of mMRC Dyspnea Scores				
Score 2, n (%)	178 (64)	276 (66)	280 (67)	265 (64)
Score 3, n (%)	91 (33)	125 (30)	128 (30)	133 (32)
Score 4, n (%)	11 (4)	17 (4)	13 (3)	15 (4)
Summary of COPD Exacerbation History[b] 12 Months Prior to Screening				
Patients requiring Oral or systemic CS with or without antibiotics, n				

	DB2113373			
	PLACEBO N = 280	**UMEC N = 418**	**VI N = 421**	**UMEC/VI FDC N = 413**
(%)				
1	57 (20)	89 (21)	88 (21)	72 (17)
2	7 (3)	20 (5)	25 (6)	16 (4)
> 2	14 (5)	11 (3)	12 (3)	11 (3)
Patients requiring hospitalization, n (%)				
1	27 (10)	46 (11)	50 (12)	33 (8)
2	2 (< 1)	3 (< 1)	3 (< 1)	5 (1)
> 2	2 (< 1)	2 (< 1)	0	1 (< 1)

COPD = chronic obstructive pulmonary disease; CS = corticosteroid; DB = double-blind; FDC = fixed-dose combination; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; GOLD = Global Initiative for Obstructive Lung Disease; ICS = inhaled corticosteroids; L = litre; mL = millilitre; mMRC = modified Medical Research Council; n = number of patients with event; N = number of patients; SALB = salbutamol; SD = standard deviation; UMEC = umeclidinium; UMEC/VI = umeclidinium/vilanterol; VI = vilanterol.

[a] Reversible refers to increase in FEV_1 of ≥ 12% and ≥ 200 mL following administration of salbutamol. Non-reversible means an increase in FEV_1 of < 200 mL or a ≥ 200 mL increase that was < 12% from pre-salbutamol FEV_1.

[b] Patients with exacerbation within 12 weeks of screening were excluded from the study.

Source: Clinical Study Report for DB2113373.[9]

TABLE 12: SUMMARY OF BASELINE CHARACTERISTICS: UMECLIDINIUM/VILANTEROL VERSUS TIOTROPIUM MONOTHERAPY

	DB2113360			DB2113374		ZEP117115	
	VI N = 209	UMEC/VI FDC N = 212	TIO N = 208	UMEC/VI FDC N = 217	TIO N = 215	UMEC/VI FDC N = 454	TIO N = 451
Demographics							
Age years, mean (SD)	63.2 (9.10)	63.0 (8.67)	62.6 (9.39)	65 (8.62)	65.2 (8.30)	61.9 (8.41)	62.7 (8.50)
Male gender, n (%)	143 (68)	148 (70)	140 (67)	140 (65)	153 (71)	310 (68)	303 (67)
Caucasian	184 (88)	182 (86)	177 (85)	164 (76)	163 (76)	439 (97)	442 (98)
Smoking History							
Current smoker, n (%)	106 (51)	98 (46)	99 (48)	92 (42)	102 (47)	270 (59)	243 (54)
Pack-years, mean (SD)	41.6 (25.36)	44.8 (27.65)	41.9 (24.44)	47.8 (26.13)	54.0 (31.59)	44.1 (24.44)	44.4 (25.03)
Spirometry Measure							
Pre-bronchodilator FEV_1 (L), mean (SD)	1.327 (0.4967)	1.314 (0.4869)	1.298 (0.5021)	1.170 (0.4655)	1.175 (0.4287)	1.261 (0.4603)	1.262 (0.4773)
Post-SALB FEV_1 (L), mean (SD)	1.449 (0.4795)	1.441 (0.4745)	1.415 (0.5025)	1.322 (0.4899)	1.328 (0.4310)	1.409 (0.4854)	1.414 (0.5036)
Pre-bronchodilator FEV_1/FVC, mean (SD)	47.605 (10.8125)	46.900 (11.0214)	47.827 (11.7717)	45.452 (11.9435)	44.998 (11.8806)	46.845 (10.5482)	46.229 (10.9394)
Post-SALB FEV_1/FVC, mean (SD)	48.173 (10.9416)	47.673 (11.0588)	48.342 (11.8678)	46.232 (11.3722)	45.804 (11.6544)	47.820 (10.7846)	47.396 (10.9173)
Post-SALB per cent predicted FEV_1 (%), mean (SD)	47.7 (12.65)	48.0 (12.94)	47.8 (13.36)	47.7 (13.55)	47.4 (13.10)	46.2 (13.02)	46.5 (12.76)
Per cent reversibility to SALB (%), mean (SD)	11.3 (13.74)	12.4 (14.97)	10.8 (13.62)	14.9 (14.95)	15.5 (15.55)	13.2 (13.36)	13.6 (13.09)
Reversibility[a] to SALB (mL), mean (SD)	119.6 (177.72)	128.6 (185.93)	115.9 (158.9)	149.9 (161.39)	152.7 (149.74)	147.5 (149.92)	152.2 (155.04)
COPD Severity (GOLD Stage), n (%)							
Stage II	94 (46)	104 (49)	96 (47)	106 (49)	103 (48)	185 (41)	190 (42)
Stage III	91 (44)	85 (40)	87 (42)	83 (38)	83 (39)	207 (46)	206 (46)
Stage IV	21 (10)	22 (10)	23 (11)	27 (13)	28 (13)	62 (14)	55 (12)
Reversible to SALB[a] patients, n (%)	98 (48)	113 (54)	99 (49)	64 (30)	60 (28)	124 (27)	142 (31)
ICS users, n (%)	84 (40)	93 (44)	93 (45)	103 (47)	115 (53)	247 (54)	237 (53)
mMRC dyspnea score, mean (SD)	2.4 (0.54)	2.4 (0.59)	2.4 (0.53)	2.4 (0.58)	2.5 (0.58)	2.4 (0.53)	2.4 (0.52)

	DB2113360			DB2113374		ZEP117115	
	VI N = 209	UMEC/VI FDC N = 212	TIO N = 208	UMEC/VI FDC N = 217	TIO N = 215	UMEC/VI FDC N = 454	TIO N = 451
Distribution of mMRC Dyspnea Scores							
Score 2, n (%)	135 (65)	137 (65)	138 (66)	139 (64)	121 (56)	286 (63)	280 (62)
Score 3, n (%)	68 (33)	64 (30)	65 (31)	68 (31)	85 (40)	159 (35)	165 (37)
Score 4, n (%)	6 (3)	11 (5)	5 (2)	10 (5)	9 (4)	9 (2)	6 (1)
Summary of COPD Exacerbation History[b] 12 Months Prior to Screening							
Patients requiring oral or systemic CS with or without antibiotics, n (%)							
1	51 (24)	50 (24)	52 (25)	41 (19)	43 (20)	58 (13)	66 (15)
2	12 (6)	13 (6)	14 (7)	11 (5)	10 (5)	11 (2)	9 (2)
> 2	2 (< 1)	1 (< 1)	4 (2)	8 (4)	13 (6)	1 (< 1)	5 (1)
Patients requiring hospitalization, n (%)							
1	28 (13)	29 (14)	32 (15)	8 (4)	14 (7)	33 (7)	27 (6)
2	6 (3)	2 (< 1)	7 (3)	1 (< 1)	0	1 (< 1)	1 (< 1)
> 2	0	0	0	0	0	0	0

COPD = chronic obstructive pulmonary disease; CS = corticosteroid; DB = double-blind; FDC = fixed-dose combination; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; GOLD = Global Initiative for Obstructive Lung Disease; ICS = inhaled corticosteroids; L = litre; mL = millilitre; mMRC = modified Medical Research Council; n = number of patients with event; N = number of patients; SALB = salbutamol; SD = standard deviation; TIO = tiotropium; UMEC = umeclidinium; UMEC/VI = umeclidinium/vilanterol; VI = vilanterol.

[a] Reversible refers to increase in FEV_1 of ≥ 12% and ≥ 200 mL following administration of salbutamol. Non-reversible means an increase in FEV_1 of < 200 mL or a ≥ 200 mL increase that was < 12% from pre-salbutamol FEV_1.

[b] Patients with exacerbation within 12 weeks of screening were excluded from the study.

Source: Clinical Study Reports for DB2113360, DB2113374, and ZEP117115.[8,10]

TABLE 13: SUMMARY OF BASELINE CHARACTERISTICS: CROSSOVER STUDIES

	DB2114417	DB2114418
	ITT Population N = 348	ITT Population N = 307
Demographics		
Age years, mean (SD)	61.6 (8.25)	62.6 (7.88)
Range	(41, 81)	(43, 84)
Male gender, n (%)	195 (56)	168 (55)
Caucasian	336 (97)	298 (97)
Smoking History		
Current smoker	220 (63)	186 (61)
Pack-years, mean (SD)	48.7 (25.27)	47.4 (24.73)
Spirometry Measure		
Pre-bronchodilator FEV_1 (L), mean (SD)	1.400 (0.4485)	1.322 (0.4212)
Post-SALB FEV_1 (L), mean (SD)	1.540 (0.4182)	1.509 (0.4170)
Pre-bronchodilator FEV_1/FVC, mean (SD)	47.994 (10.5669)	46.351(10.1150)
Post-SALB FEV_1/FVC, mean (SD)	49.316 (10.2181)	47.852 (10.1596)
Post-SALB per cent predicted FEV_1 (%), mean (SD)	51.3 (9.69)	51.3 (9.97)

	DB2114417	DB2114418
	ITT Population N = 348	**ITT Population N = 307**
Per cent reversibility to SALB (%), mean (SD)	12.6 (15.56)	16.2 (13.96)
Reversibility to SALB (mL), mean (SD)	139.8 (180.31)	187.6 (155.12)
COPD Severity (GOLD Stage), N (%)		
Stage I	0	2 (< 1)
Stage II	185 (53)	158 (52)
Stage III	163 (47)	143 (47)
Stage IV	0	1 (< 1)
Reversible[a] patients, n (%)	120 (34)	118 (39)
ICS users, n (%)	98 (28)	121 (39)
Dyspnea Score		
mMRC dyspnea score, mean (SD)	2.3 (0.49)	2.3 (0.52)
Distribution of mMRC Dyspnea Scores		
Score 2, n (%)	233 (67)	224 (73)
Score 3, n (%)	112 (32)	74 (24)
Score 4, n (%)	3 (< 1)	9 (3)
Summary of COPD Exacerbation History[b] 12 Months Prior to Screening		
Patients requiring oral or systemic CS with or without antibiotics, n (%)		
1	45 (13)	68 (22)
2	12 (3)	10 (3)
> 2	4 (1)	8 (3)
Patients requiring hospitalization, n (%)		
1	12 (3)	24 (8)
2	2 (< 1)	0
> 2	0	0

COPD = chronic obstructive pulmonary disease; CS = corticosteroid; DB = double-blind; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; GOLD = Global Initiative for Obstructive Lung Disease; ICS = inhaled corticosteroids; ITT = intention-to-treat; L = litre; mL = millilitre; mMRC = modified Medical Research Council; n = number of patients with event; N = number of patients; SALB = salbutamol; SD = standard deviation.

[a] Reversible refers to increase in FEV_1 of ≥ 12% and ≥ 200 mL following administration of salbutamol. Non-reversible means an increase in FEV_1 of < 200 mL or a ≥ 200 mL increase that was < 12% from pre-salbutamol FEV_1.

[b] Patients with exacerbation within 12 weeks of screening were excluded from the study.

Source: Clinical Study Reports for DB2113360, DB2113374, and ZEP117115.[8,10]

3.2.3 Interventions

UMEC/VI was the intervention of interest for this review. The interventions were administered in a DB fashion with neither the patient nor the study physician knowing which study drug the patient was receiving through the entire duration of treatment phases of the trials. A patient was not to continue in the study if the treatment code was unblinded. All the TIO-controlled studies had a double-dummy design, though TIO was administered through HandiHaler while all the others were administered through Ellipta DPI. No information was provided concerning training of patients on how to use the inhaler devices and it is unclear whether the patients actually demonstrated that they knew how to use the devices before initiating therapy.

In the DB2113373 trial, eligible patients were randomized to UMEC/VI, UMEC 62.5 mcg, VI 25 mcg, and placebo treatment groups in a 3:3:3:2 ratio. All treatments were administered by inhalation once daily in the morning using Ellipta DPIs that were identical in appearance and provided a total of 30 doses. All participants received supplemental salbutamol to be used on an "as-needed" basis (rescue medication) throughout the study.

In studies DB2113360, DB2113374, and ZEP117115, eligible patients were randomized in equal proportions in UMEC/VI and TIO for 24 weeks. Study DB2113360 included VI 25 mcg as another treatment group. Studies DB2113360 and DB2113374 also included treatment groups that received UMEC/VI 125 mcg/25 mcg (DB2113360 and DB2113374) or UMEC 125 mcg alone (DB2113374). As mentioned previously, the UMEC/VI 125 mcg/25 mcg and UMEC 125 mcg treatment groups were not included in the review because they are not approved for use in COPD by Health Canada. All patients were provided with a salbutamol metered-dose inhaler (MDI) for use as rescue medication throughout the run-in and study treatment periods. Each patient was given two inhalers: a preloaded Ellipta DPI and a HandiHaler dry powder inhaler with capsules, for once-daily administration of one active treatment and one placebo treatment. UMEC/VI 62.5 mcg/25 mcg and VI 25 mcg were administered through Ellipta DPI for oral inhalation. Both the TIO and placebo blister packages were covered with opaque over-labels, the HandiHalers were covered with labels to mask any identifying marks on the inhaler, and medications were dispensed by a third party at the study site not involved in efficacy or safety end points that could be influenced by knowledge of study treatment assignment. UMEC/VI 62.5 mcg/25 mcg or VI 25 mcg administered through Ellipta DPI was complemented with placebo once daily through HandiHaler, while TIO 18 mcg once daily through HandiHaler was paired with placebo once daily through Ellipta DPI. Participants were instructed to take one dose each morning from both the Ellipta DPI and the HandiHaler.

In both studies (DB2114417 and DB2114418) that investigated the effects of study drug on exercise tolerance in COPD patients, eligible patients were randomized according to the sequence in Table 10 to receive a sequence consisting of two of the following treatments: UMEC/VI 125 mcg/25 mcg, UMEC/VI 62.5 mcg/25 mcg, UMEC 125 mcg, UMEC 62.5 mcg, VI 25 mcg, or placebo once daily through Ellipta DPI, with each treatment administered for 12 weeks separated by a 14-day washout period. All patients were provided with a salbutamol MDI for use as recue medication throughout the run-in, washout, and study treatment periods. All study drugs were delivered through Ellipta DPIs identical in appearance, each providing a total of 30 doses.

In four of the included studies (DB2113373, DB2113360, DB2113374, and ZEP117115), nearly half of the patients reported use of a concomitant on-treatment COPD medication not administered for an exacerbation (Table 17, Table 18). The proportion of patients in the exercise tolerance studies (DB2114417 and DB2114418) who reported use of a concomitant on-treatment COPD medication not administered for an exacerbation was generally lower (22% to 45%; Table 19). The most common class of concomitant on-treatment COPD medications was inhaled corticosteroids (Table 17, Table 18, and Table 19).

3.2.4 Outcomes

a) Mortality or Mortality Due to COPD

Mortality was listed for the intention-to-treat (ITT) population in each study according to treatment groups. Specific cause of death was reported in many cases but not all.

b) Health Care Resource Utilization

Items evaluated under health care resource utilization included contact with health care provider, emergency room visits, and hospitalization, all of which were patient-reported. In addition to an overall summary score, it is also possible to calculate scores for the individual domains of Symptoms, Activity, and Impacts.

c) Exacerbation

According to the investigators, none of the included studies was designed to evaluate the effect of treatments on COPD exacerbations. A COPD exacerbation was defined as an acute worsening of symptoms of COPD requiring the use of any treatment beyond the study drug or rescue salbutamol. This included the use of antibiotics, systemic corticosteroids, and/or emergency treatment or hospitalization. Patients who experienced a COPD exacerbation during the treatment period were to be withdrawn from the study.

d) Quality of Life

In all four parallel-group studies (DB2113373, DB2113360, DB2113374, and ZEP117115),[6,7,9,11] health-related quality of life (HRQoL) assessments were done using the St. George's Respiratory Questionnaire (SGRQ). The SGRQ is a disease-specific questionnaire designed to measure the impact of respiratory disease and its treatment on patients' HRQoL. It consists of 50 items and was specifically developed for patients with chronic airflow limitation. The 50 items of the questionnaire are divided into three dimensions: Symptoms (eight items measuring distress due to respiratory symptoms), Activity (16 items measuring the effect of disturbances on mobility and physical activity), and Impacts (26 items measuring the psychosocial impact of the disease).[21] Items are weighted using empirically derived weights in order to determine the total SGRQ, which ranges from 0 to 100, where 0 indicates no impairment and 100 indicates worst possible health.[21,22] The generally accepted minimal clinically important difference (MCID) for a change in total SGRQ from baseline is 4.0 units of change (Table 26), while a decrease in scores indicates an increase in HRQoL.[23] APPENDIX 5 provides further details.

In addition to the SGRQ, two of the included studies (DB2113360 and DB2113374) assessed health outcomes using the EuroQol 5-Dimensions Questionnaire (EQ-5D) instrument. The EQ-5D is a standardized, self-administered, non–disease-specific instrument for describing and valuing health states that can be used across all disease areas and states of health. The EQ-5D is a three-level scale, ranging from –1 (worst possible health) to 1 (best possible health) with estimated MCID ranges of 0.03 to 0.08.

e) Spirometry

In four of the included studies (DB2113373, DB2113360, DB2113374, and ZEP117115),[6,7,9,11] the primary efficacy end point was trough FEV_1 on treatment day 169, defined as the mean of the FEV_1 values obtained 23 hours and 24 hours after dosing on treatment day 168 (i.e., at the week 24 visit).[6,7,9,11] All patients had spirometry performed at screening and at each scheduled clinic visit during the treatment period. For FEV_1 and FVC determinations, at least three acceptable spirometry efforts (with no more than eight) were obtained and the largest FEV_1 was used, even if it did not come from the same effort. An acceptable spirometry effort was defined as one with a satisfactory start and end of test, and free from artifacts due to cough, early termination, poor effort, obstructed mouthpiece, equipment malfunction, or other reasons.[6,7,9,11]

All sites assessed spirometry using standardized equipment that met or exceeded the minimal performance recommendations of the American Thoracic Society (ATS) and following this procedure:

- Started between 6:00 a.m. and 10:00 a.m.
- After completing Baseline Dyspnea Index (BDI) or Transition Dyspnea Index (TDI) and health outcomes assessments
- After withholding salbutamol for four hours or more (for all visits)
- After withholding the morning dose of blinded study drug (for visit 3 through visit 8)
- Patients were to refrain from smoking for one hour prior to each pulmonary function test
- Patients were to abstain from drinking beverages with high caffeine, such as tea and coffee, for two hours prior to each pulmonary function test.

Post-dose measurements were made as close to the scheduled time points as possible.

f) Dyspnea

TDI focal score at week 24 was an efficacy outcome in three of the parallel studies (DB2113373, DB2113360, and DB2113374) but not in and ZEP117115.[6,7,9,11] The TDI is an interviewer-administered instrument used to measure change from baseline in the severity of breathlessness in patients. When used to determine breathlessness in patients at baseline, it is called BDI. The BDI and TDI were performed prior to spirometry testing at the study visits specified in the Time and Events table of the studies. The scores in both indexes evaluated ratings for three different categories: Functional Impairment, Magnitude of Task, and Magnitude of Effort. These domains 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 more deterioration in severity of dyspnea. Both indices have been validated in patients with respiratory disease with MCID of 1 unit (see Appendix 3 for details). The same person conducted all interviews for each patient throughout the study, and the interviewer was blinded to other parameters evaluated for each patient on the visit day the index was administered. Comments from patients were recorded on a worksheet at the baseline interview (BDI) and served as reference during subsequent visits for completion of the TDI.

In the crossover exercise endurance studies, dyspnea on exercise (the exercise dyspnea scale [EDS]) was assessed using a 10-point modified Borg scale that was assessed at two-minute intervals during the endurance shuttle walking test (ESWT). Each patient indicated the level on the scale correlating with his or her dyspnea, and the coordinator confirmed this level verbally with the patient during the ESWT. The modified Borg scale is a categorical scale with a score from 0 to 10, where 0 represents normal breathing and 10 represents maximum dyspnea.[24] 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.[25-27] An MCID of 1 unit has been reported.[28]

g) Exercise Tolerance

The exercise endurance time (EET) was determined using ESWT. The EET was measured in seconds, with the MCID given as 45 seconds to 85 seconds.[10,11] A pre-dose ESWT was performed on study day 1 in an enclosed corridor on a flat, 10-meter-long course identified by two cones, each positioned 0.5 m from either end to allow patients to walk in an oval and thereby avoid the need for abrupt changes in direction. Post-dose ESWT was performed after completing scheduled spirometry and plethysmography assessments on pre-specified visits. For the EET, each patient walked at an individualized Endurance

Walking Speed Level predetermined for them prior to the EET. The end of the test was determined by any of the following:

- The patient, if he or she felt that he or she could not maintain the required speed
- The study coordinator, if the patient failed to complete a shuttle in the time allowed, which was the case when the patient was more than 0.5 m (about 20 inches) away from the target cone in a pre-specified time, and
  - the patient was unable to decrease the distance to the cone in three shuttles despite repeated encouragements, or
  - the distance to the cone increased on the second shuttle despite repeated encouragements
- The study coordinator, for safety reasons related to patient complaints, appearance, or data.

The number of shuttles was counted and the time the patient carried out the walk EET was recorded in seconds.

h) Harms

In all the included studies, safety assessments included reporting incidence of adverse events (AEs), serious adverse events (SAEs), and withdrawals due to adverse events (WDAEs). Valuation of vital signs (pulse rate and systolic and diastolic pressure), assessment 12-lead ECG parameters, and routine clinical laboratory assessments were performed but were not included in this report.

3.2.5 Statistical Analysis

a) Data Handling

The Mixed Model Repeated Measures (MMRM) approach was used for statistical analyses of all primary outcomes in all the included studies. Thus, FEV_1 at day 169 as well as the co-primary end points of EET and trough FEV_1 at week 12 were analyzed using the MMRM. Covariates used included baseline FEV_1, smoking status, centre group, and treatments. The model used all available trough FEV_1 and EET values recorded without explicitly imputing missing data. According to the investigators, all available post-baseline assessments up to end point were utilized and the derived treatment differences were adjusted to take missing data into account, with an assumption that data were missing at random. Secondary end points were analyzed for both the ITT and per-protocol (PP) populations. For dichotomous outcomes such as response, analysis was performed using a separate logistic regression model at each visit with covariates of treatment, BDI focal score, smoking status, and centre group.

b) Sample Size Calculations

In study D2113373, sample size was calculated to provide sufficient power for the comparison between treatment groups of the primary and secondary end points, including TDI at the two-sided 5% significance level. It was estimated that approximately 30% of patients would withdraw without providing a day 168 (week 24) assessment. The investigators determined that a sample size of 1,463 (266 patients in the placebo group and 399 in each treatment group) accounted for a 30% withdrawal rate and provided > 99% power to detect a 100 mL difference in FEV_1 between UMEC/VI and either UMEC or VI, or between an active treatment and placebo, as well as provide 90% power to detect a 1-unit difference between treatments in TDI. The residual standard deviation (SD) estimates used for the sample size calculations (210 mL for trough FEV_1 and 3.24 units for TDI) were based on MMRM analyses of a previous study of patients with COPD with the fluticasone propionate/salmeterol combination. The selected treatment differences (100 mL and 1 unit) are the generally accepted minimal clinically important difference for these end points.[6,7,9,11,29]

Using similar considerations (two-sided 5% significance level and estimates of residual standard deviation) as described for study DB213373, investigators in studies DB2113360 and DB2113374 determined that randomizing 208 patients to each treatment group accounted for a 30% withdrawal rate without data for end of study assessment and provided 98% power to detect a 100 mL difference in trough FEV_1 and 96% power to detect a difference of 1 unit in TDI between-treatment groups in each study. For study ZEP117115, sample size calculation used a two-sided 5% significance level and an estimate of residual standard deviation for trough FEV_1 of 240 mL. This was based on analysis of previous studies including DB2113373, DB2113360, and DB2113374. Allowing for a withdrawal rate of 25% without providing a week 24 assessment, the investigators determined that 450 patients in each treatment group would provide 90% power to detect a 60 mL difference between treatments in trough FEV_1. In studies DB2114417 and DB2114418, the sample size calculations used an estimate of residual standard deviation for the EET of 114 seconds based on data from a previous study, which indicated that a reasonable estimate of standard deviation for EET in a parallel-group study is 160 seconds.[8,10] The investigators determined that a study with 208 evaluable patients had 94% power to detect a 70-second difference in EET between the UMEC/VI group and placebo at the two-sided 5% significance level. The 70-second difference was considered appropriate because it had previously been considered a clinically important difference for within-patient comparisons of ETT.[8]

c) Interactions Analyses

For studies DB2113373, DB2113360, DB2113374, and ZEP117115, an assessment of whether the effect of treatment on trough FEV_1 is modified by centre grouping, smoking status, reversibility, and ICS use was performed. It was specified that further investigation and characterization of the interaction would be undertaken if these interaction terms demonstrate statistical significance at the 10% level. In studies DB2114417 and DB2114418, assessment of whether the effect of treatment on three-hour post-dose EET and trough FEV_1 modified by centre grouping, smoking status at screening, and mean walking speed or period walking speed was performed. Any interaction found to be statistically significant at the 10% level was to be further investigated and characterized. However, there was no statistical evidence of an interaction at the 10% level with treatment and any of the parameters. No formal statistical analyses of subgroups were performed.

d) Accounting for Multiplicity

A step-down closed testing procedure was applied to account for multiplicity across treatment comparisons of end points in all the studies. This method used a predefined hierarchy consisting of treatment comparisons performed for primary and secondary efficacy end points for each study. If the primary end points or secondary end points (as applicable) did not demonstrate statistical significance, all further statistical analyses were considered only descriptively. Inference for a test was dependent upon statistical significance having been achieved for previous tests in the hierarchy. In study DB2113373, the hierarchy was ordered as follows:

- UMEC/VI versus placebo
- UMEC versus placebo
- VI versus placebo
- UMEC/VI versus VI
- UMEC/VI versus UMEC

For study DB2113360, the hierarchy was ordered as:
- UMEC/VI 125 mcg/25 mcg versus TIO
- UMEC/VI 125 mcg/25 mcg versus VI 25 mcg
- UMEC/VI 62.5 mcg/25 mcg versus TIO
- UMEC/VI 62.5 mcg/25 mcg versus VI 25 mcg

For study DB2113374, the hierarchy was ordered as:
- UMEC/VI 125 mcg/25 mcg versus TIO
- UMEC/VI 125 mcg/25 mcg versus UMEC 125 mcg
- UMEC/VI 62.5 mcg/25 mcg versus TIO
- UMEC/VI 62.5 mcg/25 mcg versus UMEC 125 mcg

UMEC/VI 125 mcg/25 mcg and UMEC 125 mcg have not been discussed in this review for reasons previously provided.

For study ZEP117115, the step-down closed testing procedure in the manufacturer-provided clinical study report did not list treatment comparisons in a hierarchy. Instead, the secondary efficacy end point of 0 to 6 hours weighted mean FEV_1 on day 168 was tested if the treatment comparison for the primary efficacy end point of trough FEV_1 on day 169 demonstrated statistical significance at the 5% level. Inferences from all other comparisons with respect to other efficacy end points were made only if the treatment comparison of the secondary efficacy end point reached the 5% level of statistical significance. No further multiplicity adjustments were applied.

In studies DB2114417 and DB2114418, the hierarchy to account for multiplicity consisted of the following four treatment comparisons in the order presented:

- Three-hour post-dose EET for UMEC/VI 125 mcg/25 mcg versus placebo
- Trough FEV_1 for UMEC/VI 125 mcg/25 mcg versus placebo
- Three-hour post-dose EET for UMEC/VI 62.5 mcg/25 mcg versus placebo
- Trough FEV_1 for UMEC/VI 62.5 mcg/25 mcg versus placebo

UMEC/VI 125 mcg/25 mcg has not been discussed in this review for reasons previously provided.

e) Safety Analyses

For all the included studies,[6-11] safety analyses consisted of the number and percentage of patients who experienced at least one AE of any type, AEs within each body system, and AEs within each preferred term. Separate summaries were provided for all AEs, SAEs, and AEs leading to withdrawal.

Analysis Populations

The following patient populations were used for primary and secondary analysis in all the studies.[6-11]

The ITT population comprised all patients randomized to treatment who received at least one dose of randomized study drug in the treatment period. Randomized patients were assumed to have received study drug unless definitive evidence to the contrary existed. The ITT population constituted the primary population for all data analyses. Outcomes were reported according to the randomized treatment allocation. For study DB2113373, a Twenty-Four Hour (TFH) population was defined as a subset of the ITT population for whom 24-hour data were collected for spirometry and Holter monitoring.

The PP population consisted of all patients in the ITT population who were not identified as full protocol deviators. Receipt of a study treatment other than the randomized treatment was considered a protocol deviation from the time of receiving incorrect treatment onward. Patients identified as partial protocol deviators were included in the PP population but had their data excluded from PP analyses from the time of deviation onward. Patients with time-point–specific protocol deviations were included in the PP population but had the affected data excluded from PP analyses. The PP population was used for confirmatory analyses of the primary and secondary efficacy end points only, irrespective of how many patients were in the PP population. Full, partial, and time-point–specific deviations were defined in the Reporting and Analysis Plan (RAP) for each study, and the decision to exclude a patient from the PP population or a patient's data from PP analyses was made prior to breaking of the blind.

Safety analyses, summaries, figures, and listings were performed on the ITT population.

3.3 Patient Disposition

Discontinuation rates were generally high across studies. Where placebo was used as a comparator, discontinuations were generally higher in the placebo group (Table 14, Table 16). Between UMEC/VI and TIO, a trend of discontinuation rates could not be established with regard to which treatment had more (Table 15). In the three studies that compared UMEC/VI with TIO, one reported equal discontinuation rates (15%),[6] another had a lower discontinuation rate for TIO (18% versus 25%),[7] and the third reported a lower discontinuation rate in favour of UMEC/VI (12% versus 14%).[11]

For patients on placebo, the most common reason for discontinuation was lack of efficacy. For the active treatments, the most common reason for discontinuation was, in general, adverse events.

TABLE 14: PATIENT DISPOSITION: UMECLIDINIUM/VILANTEROL FIXED-DOSE COMBINATION VERSUS PLACEBO, UMECLIDINIUM, AND VILANTEROL MONOTHERAPY

	DB2113373			
	Placebo	**UMEC**	**VI**	**UMEC/VI**
Screened, N	2,210			
Randomized, N (%)	280 (100)	418 (100)	421 (100)	413 (100)
Completed, n (%)	204 (73)	324 (78)	318 (76)	332 (80)
Discontinued, n (%)	76 (27)	94 (22)	103 (24)	81 (20)
Adverse event, n (%)	9 (3)	34 (8)	24 (6)	23 (6)
Lack of efficacy, n (%)	37 (13)	20 (5)	32 (8)	20(5)
Protocol deviation, n (%)	4 (1)	7 (2)	5 (1)	6 (1)
Reached stop criteria, n (%)	9 (3)	13 (3)	24 (6)	15 4)
ECG abnormality	5 (2)	7 (2)	17 (4)	12 3)
Lab abnormality	0	2 (<1)	2 (<1)	0
Lost to follow-up, n (%)	1 (<1)	0	3 (<1)	2 (<1)
Withdrawal of consent	16 (6)	20 (5)	15 (4)	15 (4)
Patient relocated, n (%)	3 (1)	2 (<1)	2 (<1)	2 (<1)
Frequency of visits, n (%)	3 (1)	1 (<1)	3 (<1)	2 (<1)
Burden of procedures, n (%)	1 (<1)	4 (<1)	2 (<1)	1 (<1)
Other	7 (3)	10 (2)	6 (1)	6 (1)
ITT, n (%)	280 (100)	418 (100)	421 (100)	413 (100)
PP, n (%)	233 (83)	362 (87)	372 (88)	363 (88)
Safety, n (%)	280	418	421	413

DB = double-blind; ECG = electrocardiogram; ITT = intention-to-treat; Lab = laboratory; n = number of patients with event; N = number of patients; PP = per-protocol, UMEC = umeclidinium; UMEC/VI = umeclidinium/vilanterol; VI = vilanterol.
Source: Clinical Study Report for DB2113373.[9]

TABLE 15: PATIENT DISPOSITION: UMECLIDINIUM/VILANTEROL FIXED-DOSE COMBINATION VERSUS TIOTROPIUM MONOTHERAPY

	DB2113360			DB2113374		ZEP117115	
	VI	UMEC/VI	TIO	UMEC/VI	TIO	UMEC/VI	TIO
Screened, N	1,141			1,191		1,191	
Randomized, N (%)	209 (100)	212 (100)	208 (100)	218 (100)	215 (100)	454 (100)	451 (100)
Completed, N (%)	165 (79)	181 (85)	177 (85)	163 (75)	176 (88)	401 (88)	388 (86)
Discontinued, N (%)	44 (21)	31 (15)	31 (15)	54 (25)	39 (18)	53 (12)	63 (14)
Adverse event	10 (5)	10 (5)	9 (4)	20 (9)	11 (5)	18 (4)	14 (3)
Lack of efficacy	17 (8)	9 (4)	7 (3)	12 (6)	13 (6)	15 (3)	29 (6)
Withdrawal of consent	7 (3)	8 (4)	9 (4)	10 (5)	6 (3)	14 (3)	11 (2)
ECG abnormality	2 (< 1)	3 (1)	5 (2)	11 (5)	6 (3)	NR	NR
Protocol deviation	7 (3)	1 (< 1)	0	4 (2)	1 (< 1)	3 (< 1)	7 (2)
Lost to follow-up	1 (< 1)	1 (< 1)	1 (< 1)	0	2 (< 1)	3 (< 1)	2 (< 1)
Burden of procedures	1 (< 1)	2 (< 1)	4 (2)	2 (< 1)	1 (< 1)	1 (< 1)	1 (< 1)
Patient relocated	1 (< 1)	1 (< 1)	0	1 (< 1)	0	2 (< 1)	3 (< 1)
Frequency of visits	2 (< 1)	0	1 (< 1)	2 (< 1)	1 (< 1)	1 (< 1)	1 (< 1)
Other	4 (2)	6 (3)	4 (2)	5 (2)	4 (2)	11 (2)	6 (1)
ITT, N	209	212	208	217	215	454	451
PP, N (%)	182 (89)	179 (86)	184 (91)	187 (86)	194 (90)	430 (95)	428 (95)
Safety, N	209	212	208	217	215	454	451

DB = double-blind; ECG = electrocardiogram; ITT = intention-to-treat; N = number of patients; PP = per-protocol; TIO = tiotropium; UMEC = umeclidinium; UMEC/VI = umeclidinium/vilanterol; VI = vilanterol.
Source: Clinical Study Reports for DB2113360, DB2113374, and ZEP117115.[6,7,11]

TABLE 16: PATIENT DISPOSITION: CROSSOVER STUDIES

	DB2114417				DB2114418			
	Placebo	**UMEC**	**VI**	**UMEC/VI**	**Placebo**	**UMEC**	**VI**	**UMEC/VI**
Screened, N	596				634			
Randomized,[a] N (%)	170 (100)	49 (100)	76 (100)	152 (100)	151 (100)	40 (100)	64 (100)	130 (100)
Completed,[b] N (%)	148 (87)	43 (88)	64 (84)	131 (86)	120 (79)	38 (95)	56 (87)	117 (90)
Discontinued, N (%)	22 (13)	6 (12)	12 (16)	21 (14)	31 (21)	2 (5)	8 (13)	14 (11)
Adverse event	4 (2)	2 (4)	8 (10)	6 (4)	6 (4)	1 (3)	3 (5)	4 (3)
Lack of efficacy	6 (4)	1 (2)	1 (1)	6 (4)	6 (4)	0	3 (5)	3 (2)
ECG abnormality	0	0	0	0	0	0	1 (< 1)	1 (< 1)
Lab abnormality	0	1 (2)	0	2 (1)	0	0	0	0
Protocol deviation	0	0	1 (1)	0	2 (1)	0	1 (2)	1 (< 1)
Lost to follow-up	2 (1)	0	1 (1)	0	0	0	0	1 (< 1)
Withdrawal of consent	0	2 (4)	2 (3)	1 (< 1)	5 (3)	0	1 (2)	3 (2)
Burden of procedures	0	1 (2)	2 (3)	0	2 (1)	0	0	1 (<1)
Patient relocated	0	0	0	1 (<1)	2 (1)	0	0	1 (<1)
Frequency of visits	0	0	0	0	0	0	0	0
Other	0	1 (2)	0	0	1 (<1)	0	1 (2)	1 (<1)
ITT, N	348				307			
PP, N	333				281			
Safety, N	348				307			

DB = double-blind; ECG = electrocardiogram; ITT = intention-to-treat; Lab = laboratory; N = number of patients; PP = per-protocol; UMEC = umeclidinium; UMEC/VI = umeclidinium/vilanterol; VI = vilanterol.

[a] Each randomized patient had two treatment periods separated by a 14-day washout period. Data for the two periods have been pooled, where applicable.

[b] A patient was considered to have completed the treatment period if he or she completed a week 12 visit for the period of interest.

Source: Clinical Study Reports for DB2114417 and DB2114418.[8,10]

3.4 Exposure to Study Treatments

Exposure was similar between studies and across treatment groups.[6-11] The median duration of exposure ranged from 167 days to 168 days (Table 17, Table 18). In study ZEP117115, the median duration of exposure was identical (168 days) for both the UMEC 62.5 mcg and TIO treatment groups. The distribution of length of exposure was also similar across treatment groups. The median duration of exposure was [redacted] days for all treatment groups in studies DB2114417 and DB2114418 (Table 19). This was shorter compared with the other studies because the duration of each treatment period was 12 weeks. The mean treatment compliance was high across all studies, ranging from 97.8% to 101%. For each study, compliance was generally similar between treatment groups (see Table 18 and Table 19). In four of the included studies (DB2113373, DB2113360, DB2113374, and ZEP117115), nearly half of the patients reported use of a concomitant on-treatment COPD medication not administered for an exacerbation (Table 17, Table 18). The proportion of patients in the exercise tolerance studies

(DB2114417 and DB2114418) who reported use of a concomitant on-treatment COPD medication not administered for an exacerbation was generally lower ([redacted]% to [redacted]%; Table 19). This is probably because generally the patients involved in these exercise studies had less severe COPD conditions than those in the other studies. In study DB2114417, concomitant on-treatment COPD medication use was comparable between placebo and UMEC/VI, while in study DB2114418 the UMEC/VI treatment group had a lower rate of concomitant on-treatment COPD medication use (Table 19). The most common class of concomitant on-treatment COPD medications was inhaled corticosteroids (Table 17, Table 18, and Table 19).

TABLE 17: SUMMARY OF EXPOSURE TO STUDY DRUGS, TREATMENT COMPLIANCE, AND CONCOMITANT ON-TREATMENT CHRONIC OBSTRUCTIVE PULMONARY DISEASE MEDICATION — UMECLIDINIUM/VILANTEROL FIXED-DOSE COMBINATION VERSUS PLACEBO, UMECLIDINIUM, AND VILANTEROL MONOTHERAPY

	DB2113373			
	Placebo N = 280	**UMEC 62.5 mcg N = 418**	**VI 25 mcg N = 421**	**UMEC/VI 62.5 mcg/25 mcg N = 413**
Exposure (days), n				
Median (range)	167.0 (1, 177)	168.0 (1, 179)	168.0 (1, 206)	168.0 (1, 177)
Length of Exposure (days)	**Number (%) of Patients**			
1 to 84	43 (15)	54 (13)	53 (13)	42 (10)
85 to 168	144 (51)	210 (50)	231 (55)	184 (45)
> 168	93 (33)	154 (37)	137 (33)	187 (45)
Compliance (%)				
Mean (SD)	98.3 (7.97)	99.8 (23.28)	98.4 (7.81)	98.5 (4.94)
Compliance Category, n (%)				
< 80%	1 (< 1)	4 (< 1)	5 (1)	0
≥ 80% to < 95%	44 (17)	53 (13)	55 (14)	48 (12)
≥ 95% to ≤ 105%	217 (82)	333 (82)	330 (81)	344 (86)
> 105% to ≤ 120%	3 (1)	12 (3)	15 (4)	6 (2)
> 120%	1 (< 1)	4 (< 1)	2 (< 1)	2 (< 1)
On-treatment COPD Concomitant Medications				
Any medication, n (%)	140 (50)	230 (55)	223 (53)	219 (53)
Inhaled corticosteroid, n (%)	131 (47)	210 (50)	205 (49)	205 (50)
Mucolytics	6 (2)	18 (4)	14 (3)	9 (2)
Oxygen	7 (3)	6 (1)	8 (2)	11 (3)
SABA	3 (1)	3 (< 1)	5 (1)	8 (2)
SAMA	5 (2)	3 (< 1)	4 (< 1)	5 (1)
LAMA	4 (1)	1 (< 1)	0	6 (1)
Antibiotics	1 (< 1)	2 (< 1)	3 (< 1)	3 (< 1)

COPD = chronic obstructive pulmonary disease; DB = double-blind; LAMA = long-acting muscarinic antagonist; mcg = microgram; n = number of patients with event; N = number of patients; SABA = short-acting beta2-agonist; SAMA = short-acting muscarinic antagonist; SD = standard deviation; UMEC = umeclidinium; UMEC/VI = umeclidinium/vilanterol; VI = vilanterol.
Source: Clinical Study Report for DB2113373.[9]

TABLE 18: SUMMARY OF EXPOSURE TO STUDY DRUGS, TREATMENT COMPLIANCE, AND CONCOMITANT ON-TREATMENT CHRONIC OBSTRUCTIVE PULMONARY DISEASE MEDICATION — UMECLIDINIUM/VILANTEROL FIXED-DOSE COMBINATION VERSUS TIOTROPIUM, UMECLIDINIUM, AND VILANTEROL MONOTHERAPY

	DB2113360			DB2113374		ZEP117115	
	VI 25 mcg N = 209	UMEC/VI 62.5 mcg/25 mcg N = 212	TIO N = 208	UMEC/VI 62.5 mcg/ 25 mcg N = 217	TIO N = 215	UMEC 62.5 mcg N = 418	UMEC/VI 62.5 mcg/ 25 mcg N = 413
Exposure (days), n							
Median (range)	167.0 (1, 179)	168.0 (1, 176)	168.0 (1, 175)	167.0 (1, 175)	167.0 (1, 176)	168.0 (2, 199)	168.0 (1, 181)
Length of Exposure (days)	**Number (%) of Patients**						
1 to 84	24 (11)	15 (7)	21 (10)	36 (17)	28 (13)	27 (6)	39 (9)
85 to 168	116 (56)	129 (61)	134 (64)	110 (51)	124 (58)	214 (47)	238 (53)
> 168	69 (33)	68 (32)	53 (25)	71 (33)	63 (29)	213 (47)	174 (39)
Compliance (%)							
Mean (SD)	98.4 (3.08)	97.9 (8.61)	97.8 (7.11)	98.9 (8.39)	98.7 (6.08)	98.8 (4.18)	99.1 (3.67)
Compliance Category, n (%)							
< 80%	0	3 (1)	3 (1)	2 (< 1)	2 (< 1)	5 (1)	3 (< 1)
≥ 80% to < 95%	29 (14)	38 (19)	21 (10)	23 (11)	27 (13)	23 (5)	22 (5)
≥ 95% to ≤ 105%	175 (85)	162 (79)	181 (88)	181 (86)	179 (84)	415 (93)	412 (94)
> 105% to ≤ 120%	1 (< 1)	1 (< 1)	0	2 (< 1)	3 (1)	1 (< 1)	1 (< 1)
> 120%	0	1 (< 1)	0	3 (1)	2 (< 1)	0 1	(< 1)
On-treatment COPD Concomitant Medications							
Any medication, n (%)	89 (43)	96 (45)	96 (46)	113 (52)	116 (54)	259 (57)	247 (55)
Inhaled corticosteroid, n (%)	83 (40)	93 (44)	90 (43)	96 (44)	106 (49)	247 (54)	237 (53)
Mucolytics	8 (4)	3 (1)	8 (4)	22 (10)	19 (9)	11 (2)	6 (1)
Oxygen	2 (< 1)	6 (3)	5 (2)	6 (3)	6 (3)	11 (2)	7 (2)
SABA	2 (< 1)	1 (< 1)	1 (< 1)	3 (1)	1 (< 1)	1 (< 1)	1 (< 1)
SAMA	2 (< 1)	1 (< 1)	3 (1)	0	1 (< 1)	0	2 (< 1)
LAMA	0	0	1 (< 1)	1 (< 1)	0	NR	NR
Antibiotics	NR	NR	NR	1 (< 1)	1 (< 1)	NR	NR

COPD = chronic obstructive pulmonary disease; DB = double-blind; LAMA = long-acting muscarinic antagonist; mcg = microgram; n = number of patients with event; N = number of patients; NR = not reported; SABA = short-acting beta2-agonist; SAMA = short-acting muscarinic antagonist; SD = standard deviation; TIO = tiotropium; UMEC = umeclidinium; UMEC/VI = umeclidinium/vilanterol; VI = vilanterol.
Source: Clinical Study Reports for DB2113360, DB2113374, and ZEP117115.[6,7,11]

TABLE 19: SUMMARY OF EXPOSURE TO STUDY DRUGS, TREATMENT COMPLIANCE, AND CONCOMITANT ON-TREATMENT CHRONIC OBSTRUCTIVE PULMONARY DISEASE MEDICATION — CROSSOVER STUDIES

	DB2114417				DB2114418			
	Placebo N = 170	UMEC 62.5 mcg N = 49	VI 25 mcg N = 76	UMEC/VI 62.5 mcg/ 25 mcg N = 152	Placebo N = 151	UMEC 62.5 mcg N = 40	VI 25 mcg N = 64	UMEC/VI 62.5 mcg/ 25 mcg N = 130
Exposure (days), n								
Median (range)	[redacted]							
Compliance (%)								
Mean (SD)	[redacted]							
Compliance Category, n (%)								
< 80%	[redacted]							
≥ 80% to < 95%	[redacted]							
≥ 95% to ≤ 105%	[redacted]							
> 105% to ≤ 120%	[redacted]							
> 120%	[redacted]							
On-treatment COPD Concomitant Medications								
Any medication, n (%)	[redacted]							
Inhaled corticosteroid, n (%)	[redacted]							
Mucolytics	[redacted]							
Oxygen	[redacted]							
SABA	[redacted]							
SAMA	[redacted]							
LAMA	[redacted]							

COPD = chronic obstructive pulmonary disease; DB = double-blind; LAMA = long-acting muscarinic antagonist; mcg = microgram; n = number of patients with event; N = number of patients; SABA = short-acting beta2-agonist; SAMA = short-acting muscarinic antagonist; SD = standard deviation; UMEC = umeclidinium; UMEC/VI = umeclidinium/vilanterol; VI = vilanterol.
Note: Data redacted at the request of manufacturer.
Source: Clinical Study Reports for DB2114417 and DB2114418.[8,10]

3.5 Critical Appraisal

3.5.1 Internal Validity

Baseline characteristics of study participants were generally similar among studies and across treatment groups in each study with respect to demographics, smoking history, COPD duration and severity, and co-existing medical conditions. The majority of patients reported no COPD exacerbations requiring hospitalization or the use of oral or systemic corticosteroids and/or antibiotics in the 12 months prior to screening, and the proportions of these patients were generally similar across treatment groups in all studies. Furthermore, the use of ICS was similar across studies, and the proportion of users and non-users was generally similar among treatment groups for each study. Therefore, although numerical

differences between treatment groups were reported, they probably did not influence the reported outcomes.

Patients in each study were assigned to blinded treatment regimens by randomization using an interactive voice response system with codes generated by a validated computerized system. The study physicians and patients were blinded to the study drug the patients were receiving. However, investigators or treating physicians could unblind a patient's treatment in case of an emergency. In that case, the patient was to be discontinued from the study, without revealing the patient's treatment assignment. Opaque over-labels and dummy inhaler devices were used where necessary to ensure the integrity of the blinding. In addition, medications were dispensed by third parties not involved in the efficacy or safety end points. The investigators reported that although the TIO and placebo capsules were closely matched in colour, the blinding of TIO in this manner was imperfect because the TIO capsules had trade markings and the placebo capsules did not. Therefore, it was unclear whether the patients could notice and correctly or incorrectly interpret this difference.

Each of the included studies had a priori sample size calculations to power the analyses to detect statistically significant differences between treatments in the primary efficacy end points. Discontinuation from studies tended to be high, ranging from 20% to 27% in study DB2113373, 12% to 25% across TIO-controlled studies, and 5% to 21% for the crossover studies. There was no clear pattern among groups, other than those receiving placebo in the placebo-controlled studies discontinued more frequently versus those on active treatment. Nevertheless, the high rate of discontinuation is a concern and a threat to the validity of the included studies; it can compromise the original random allocation of patients and disrupt the balance randomization that was intended to be achieved among groups being compared. It is unclear whether rate of withdrawals influenced the reported outcomes and in which direction.

The statistical analysis plans of each included study stated that MMRM analysis was used. MMRM includes all non-missing data for statistical analyses with an underlying assumption that data were missing at random and therefore missing data were not directly imputed in any of the analyses. This assumption of data missing at random does not seem appropriate because 2% to 10% and 0% to 13% of patients discontinued as a result of adverse effects or lack of efficacy, respectively. Thus, a non-trivial range of proportions of discontinuations was not missing at random. However, sensitivity analyses using multiple imputation methods produced results that aligned with the MMRM analyses, although it remains unclear if the underlying assumptions of these analyses were likewise satisfied.

Multiplicity was handled with a step-down hierarchical system. In two of the studies (DB2113374 and DB2114417), statistical inference could not be drawn from the comparison of UMEC/VI and comparators because a difference between treatment comparisons of higher hierarchy (UMEC/VI 125 mcg/25 mcg versus UMEC 125 mcg on trough FEV_1 in DB2113374 and UMEC/VI 125 mcg/25 mcg versus placebo on EET in DB2114417, respectively) failed to reach statistical significance.

The exercise endurance studies were crossover trials involving two treatment periods. Patients had a two-week washout period before crossing over from one treatment to the other. The basis for selecting the duration of the washout period was not given. The concern is whether there is any carry-over effect from the first period to the second. However, the clinical expert involved in the review did not think the chosen washout duration affected the validity of the results in these studies.

The studies did not describe patients as having received some type of training on use of the inhaler devices. Moreover, it was not clear whether patients actually demonstrated that they knew how to use the devices before initiating therapy. Although compliance was high in the included studies, this simply reflects the number of doses actuated rather than whether the dose was delivered optimally.

3.5.2 External Validity

Most of the patients enrolled in the studies had GOLD Stage II and GOLD Stage III COPD representing moderate to severe disease, with the exception of the crossover endurance studies, which excluded more severe patients. However, according to the clinical expert involved in this review, this is likely not unreasonable as subjecting severe or very severe patients to endurance testing would put them at undue risk for worsening COPD symptoms.

The included studies enrolled patients who were as young as 40 years, and this would be considered young for a disease that typically is diagnosed and treatment initiated in the later 50s and early 60s. Despite this relatively young minimum age for inclusion, the average age of patients was typically in the early to mid-60s, and this would be more consistent with the COPD population in Canada. Additionally, the majority of patients across the studies were male and this reflects COPD population at the time the included studies were conducted. However, with the considerable increase in the proportion of female current smokers, it is anticipated that in the near future, there may be more females than males with COPD.

In many of the included studies, the mean post-bronchodilator reversibility was around 15%, suggesting that a number of patients may have had asthma along with COPD. This might be considered to be a high degree of reversibility compared with what one would expect to see in the general COPD population. The implication is that these patients may have underlying asthma that may be more responsive to bronchodilators. As well, approximately one-half of patients were taking concurrent ICS, which may have also improved outcomes for patients with an asthmatic component; however, the distribution of ICS users at baseline did not appear to be differential among treatment groups in any of the studies.

Three of the included studies compared UMEC/VI with placebo and the individual component VI 25 mcg administered as monotherapy. While this may be of regulatory value, the clinical importance is not very clear, especially because VI 25 mcg does not yet have Health Canada approval for the management of COPD. Tiotropium, administered at the recommended dose of 18 mcg once daily, was the key comparator in three of the included studies. Although TIO monotherapy is a guideline-approved maintenance medication for COPD, a head-to-head comparison with other LABA plus LAMA combination therapy alternatives may have been more useful. However, the manufacturer-provided indirect comparison that suggested UMEC/VI is not statistically different from fluticasone/salmeterol plus tiotropium combination (IND/TIO, FLUT/SAL+TIO) or a combination of indacaterol/glycopyrronium in improving lung function (measured by change in FEV_1), the need for rescue medication use, improving HRQoL, and dyspnea symptoms for patients with COPD (APPENDIX 6).

The included studies had 24 weeks' duration or less. Although the duration is comparable to what was used in many other clinical trials in COPD, it may be insufficient for a comprehensive assessment of long-term efficacy and safety (including mortality) outcomes in a chronic condition like COPD. Furthermore, patients who experienced COPD exacerbation during the trial were withdrawn from the study. Since COPD patients may experience exacerbation at some point, it is uncertain how patients would be handled when they experience COPD while using UMEC/VI in clinical practice. Therefore, the generalizability of all the study findings to patients with COPD exacerbations is uncertain. Furthermore,

it is unknown if the findings of the exercise endurance studies would be generalizable to patients with very severe COPD, as such patients were excluded from the studies.

Many of the included studies assessed dyspnea using a scoring system; however, most used BDI/TDI scores rather than Borg dyspnea scores. According to the clinical expert, the Borg scoring system is the one more commonly used in practice; therefore, this might affect the generalizability of the dyspnea data from the included studies.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 6). See APPENDIX 4 for detailed efficacy data.

3.6.1 Mortality

The incidence of death was generally low (≤ 1%) across all the studies. In study DB2113373, a total of six patients died: two in UMEC/VI, one in UMEC 62.5 mcg, and three in VI 25 mcg groups (Table 20). There was no death reported in the placebo group. Causes of death included COPD exacerbation and respiratory failure, a case cardiac disorder (myocardial infarction), and others described as "fatal SAE of sudden death." In study DB2113360, one person died in each of the UMEC/VI and VI 25 mcg groups due to cardiac disorders. No death was reported in the TIO group (Table 21). Two patients in the TIO group died in study DB2113374 while one patient died in the UMEC/VI group. In study ZEP117115, a total of seven patients died: two in the UMEC/VI group and five in the TIO group (see Table 21 for details). No death occurred among patients in the treatment group of interest to this review in study DB2114417 (Table 22). One patient in the UMEC/VI group of study DB2114418 died due to lung cancer. There were no deaths in the other treatment groups (Table 22).

3.6.2 Health Care Resource Utilization

In study DB2113373, approximately 2% (UMEC/VI) to 5% (placebo) of patients across treatment groups had emergency room (ER) visits (Table 20). Only two patients (one in the placebo and the other in the VI 25 mcg groups) had two emergency visits, with all other patients visiting the ER once. Likewise, few patients were admitted to hospital during the study: approximately 3% (UMEC/VI) to 4% (VI) of patients across treatments. One patient in each of the UMEC 62.5 mcg and VI 25 mcg groups spent a day in the intensive care unit. No patient from the other treatment groups was in intensive care. In study DB2113360, five (approximately 2.5%) patients in the UMEC/VI and TIO groups visited the ER compared with seven (3.4%) patients in the VI 25 mcg group (Table 21). Only one patient in study DB2113360 (in the UMEC/VI group) had two ER visits; the rest visited the ER only once each. The percentage of patients admitted to hospital was low in each group, ranging from one (0.5%) patient in the UMEC/VI group to nine (4.4%) patients in the VI group. There was no intensive care service for any patients in study DB2113360. In study DB2113374, 10 (4.6%) patients in the UMEC/VI group visited the ER compared with six (2.8%) patients in the TIO group. Only one patient (in the UMEC/VI group) had two ER visits; the rest visited the ER only once each. Hospitalization occurred in 11 (5.1%) of UMEC/VI patients versus six (2.8%) of TIO patients. A patient in the UMEC/VI group utilized intensive care service with no patient from the TIO group receiving intensive care service. The remaining included studies (ZEP117115, DB2114417, and DB2114418) had no reports on total health care utilization, although they did report the number of patients who were admitted to hospital or visited the ER due to on-treatment acute exacerbation of COPD. The frequency of exacerbation-related hospitalization and ER visits were generally low in these studies, although this may be an underrepresentation of health care use.

3.6.3 Quality of Life

Four studies (DB2113373, DB2113360, DB2113374, and ZEP117115) reported on quality of life using the SGRQ instrument (MCID of 4 points). In study DB2113373, the difference in improvements in health outcomes as measured by SGRQ were statistically significant and clinically relevant in favour of the UMEC/VI group compared with placebo at day 168 (least squares [LS] mean difference [MD] –5.51 [95% confidence interval [CI], –7.88 to –3.13]; *P* < 0.001; Table 20). In each of the TIO-controlled studies (DB2113360, DB2113374, and ZEP117115), treatment with either UMEC/VI or TIO resulted in clinically relevant improvement in SGRQ scores from baseline at day 168 (Table 21). Treatment with UMEC/VI showed a greater reduction in SGRQ compared to TIO in studies DB2113374 (LS MD –0.17 [95% CI, –2.85 to 2.52]; *P* = 0.904) and ZEP117115 (LS MD –2.10 [95% CI, –3.61 to –0.59]; *P* = 0.006), while TIO showed a greater improvement in SGRQ than UMEC/VI in study DB2113360 (LS MD 0.75 [95% CI, –2.12 to 3.63]; *P* = 0.607). The clinical significance of the differences in SGRQ scores between UMEC/VI and TIO is uncertain (Table 21). In addition to the SGRQ, studies DB2113360 and DB2113374 assessed health outcomes using the EQ-5D instrument. The EQ-5D is a standardized, self-administered, non-disease-specific instrument for describing and valuing health states that can be used across all disease areas and states of health. The EQ-5D is a three-level scale ranging from –1 (worst possible health) to 1 (best possible health) with estimated MCID ranges of 0.05 to 0.08. Clinically meaningful mean improvement in EQ-5D scores from baseline was observed in the UMEC/VI treatment group at day 168 in both studies (mean [SD] 0.07 [0.203] in DB2113360 and 0.08 [0.215] in DB2113374), while the TIO treatment resulted in clinically meaningful improvement in EQ-5D scores (mean [SD] 0.08 [0.224]) from baseline in study DB2113374 only (Table 21). In both studies, the clinical significance of the differences in SGRQ scores between treatment groups was uncertain.

3.6.4 Spirometry

Study DB2113373 demonstrated that treatment with UMEC/VI resulted in statistically significant improvements in the primary efficacy end point of trough FEV_1 at day 169 compared with monotherapy using UMEC 62.5 mcg (0.052 L [95% CI, 0.017 to 0.087]; *P* = 0.004) or VI 25 mcg (0.095 L [95% CI, 0.060 to 0.130]; *P* < 0.001), and placebo (0.167 L [95% CI, 0.128 to 0.207]; *P* < 0.001; Table 20). In DB2113360, UMEC/VI demonstrated statistically significant improvement in the primary end point of trough FEV_1 at day 169 compared with TIO 18 mcg (0.09 L [95% CI, 0.039 to 0.141]; *P* < 0.001; Table 21). In DB2113374, UMEC/VI resulted in greater improvements in trough FEV_1 (0.060 L [95% CI, 0.010 to 0.109]; *P* = 0.018) at day 169 compared with TIO though not to the same extent as occurred in DB2113360 (0.060 L [95% CI, 0.010 to 0.109]; *P* = 0.018). However, in accordance with the pre-specified hierarchical statistical analysis plan for study DB2113374 (see Accounting for Multiplicity in the Statistical Analyses section), statistical significance could not be inferred because comparison of UMEC/VI 125 mcg/25 mcg with UMEC 125 failed to demonstrate significance. In study ZEP117115, UMEC/VI demonstrated statistically significant improvement in the trough FEV_1 at day 169 compared with TIO 18 mcg (112 [95% CI, 0.081 to 0.144]; *P* < 0.001; Table 21).

Change from baseline in trough FEV_1 was a co-primary outcome (with post-dose EET) in the crossover endurance studies. In study DB2114417, UMEC/VI improved trough FEV_1 by 0.211 L (95% CI, 0.172 to 0.249) at 12 weeks compared with placebo (Table 22). However, an inference of statistical significance between the two treatments could not be made because, based on the pre-specified hierarchical analysis plan, a higher order comparison between UMEC/VI 125 mcg/25 mcg and placebo in improvement in EET was not statistically significant. In the other exercise endurance study (DB2114418), treatment with UMEC/VI demonstrated statistically significant and clinically meaningful improvement in trough FEV_1 at week 12 compared with placebo (LS MD 0.243 L [95% CI, 0.202 to 0.284]; *P* < 0.001) and with VI (LS MD 0.132 L [95% CI, 0.081 to 0.183]; *P* < 0.001). UMEC/VI was also statistically significantly

improved versus UMEC, and the between-group difference almost reached the MCID of 0.1 L (LS MD 0.099 L [95% CI, 0.041 to 0.157]; *P* < 0.001).

3.6.5 Dyspnea

Transition Dyspnea Index (TDI) scores were reported in three studies (DB2113373, DB2113360, and DB2113374). In DB2113373 all the treatment groups including placebo had improvements in TDI score from baseline that exceeded the MCID of 1 unit (Table 20). The difference in TDI score between UMEC/VI and placebo was statistically significant and clinically meaningful (LS MD 1.2 [95% CI, 0.7 to 1.7]; *P* < 0.001). In studies DB2113360 and DB2113374, treatment with UMEC/VI or TIO resulted in clinically relevant improvements in TDI scores from baseline. In DB2113360, LS mean (standard error [SE]) at day 168 were 2.3 (0.2) and 2.4 (0.2) for UMEC/VI and TIO, respectively, while LS mean (SE) at day 168 in DB2113374 were 2.3 (0.3) and 2.1 (0.2), for UMEC/VI and TIO, respectively (Table 21). However, the difference in improvements in TDI score between UMEC/VI and TIO did not reach statistically significant or (unlikely) clinically meaningful level in any of the studies. The LS MD between the two treatments was –0.1 units (95% CI, –0.7 to 0.5; *P* = 0.72) in DB2113360, and 0.2 units (95% CI, –0.5 to 0.9; *P* = 0.55) in DB2113374 (Table 21). In study DB2113373, the proportion of TDI responders at day 168 was greater for UMEC/VI (58%) compared with placebo (41%; Table 20). A TDI responder at any visit was defined as a patient with a TDI focal score of at least 1 unit at that visit. The odds of being a TDI responder versus a non-responder were greater for UMEC/VI than with placebo (odds ratio [OR] 2.0 [95% CI, 1.5 to 2.8]; *P* < 0.001; Table 20). In study DB2113360, the odds of being a TDI responder versus a non-responder were lower for UMEC/VI than for TIO (OR 0.9 [95% CI, 0.6 to 1.3]; *P* = 0.464), while in study DB2113374, patients treated with UMEC/VI had greater odds (OR 1.3 [95% CI, 0.9 to 1.9], *P* = 0.198) of being responders compared with patients treated with TIO (Table 21). The difference between the treatment with UMEC/VI and TIO with respect to TDI responders was not statistically significant.

The crossover studies (DB2114417 and DB2114418) measured dyspnea on exercise using a 10-point modified Borg scale (MCID 1 unit). In study DB2114417, the LS MD between UMEC/VI and placebo was –0.05 (95% CI, –0.37 to 0.27). In study DB2114418, the LS MD between UMEC/VI and placebo was –0.36 (95% CI, –0.67 to –0.05) (Table 22).

3.6.6 Exercise Tolerance

Two studies (DB2114417 and DB2114418) assessed exercise tolerance with three-hour post-dose EET and in trough FEV_1 at week 12 as co-primary end points. The MCID for EET was reported to be between 45 seconds and 85 seconds.[8,10] In study DB2114417, the difference in improvement in three-hour post-dose EET at week 12 following treatment with UMEC/VI was not statistically significant or clinically meaningful compared with its components or placebo (UMEC/VI versus placebo; or UMEC; or VI: –21.9 [95% CI, –14.2 to 58.0]; *P* = 0.234; or –4.6 [95% CI, –57.6 to 48.4]; *P* = 0.865; or 31.9 [95% CI, –14.1 to 77.9]; *P* = 0.174, respectively; Table 22). Treatment with UMEC/VI resulted in LS mean changes from baseline in trough FEV_1 (0.178 L) at week 12 that could have been described as clinically meaningful (MCID 0.100 L) both with group and compared with placebo (LS MD 0.211 L [95% CI, 0.172 to 0.249]; *P* < 0.001; Table 22). However, statistical inference could not be made for comparisons of UMEC/VI 62.5 mcg/25 mcg and other treatment groups in study DB2114417, because the testing hierarchy (comparison between UMEC/VI 125 mcg/25 mcg and placebo on EET set a priori) failed to demonstrate statistical significance.

In DB2114418, statistically significant and clinically meaningful difference (69.4 [95% CI, 24.5 to 114.4]; *P* = 0.003) in LS mean improvements from baseline in three-hour post-dose EET were demonstrated for UMEC/VI 62.5 mcg/25 mcg compared with placebo, but not its components at week 12 (Table 22). Also,

treatment with UMEC/VI resulted in LS mean improvement from baseline in trough FEV_1 at week 12, which was statistically significant and clinically meaningful ($P < 0.001$; Table 22). UMEC/VI also demonstrated greater LS mean changes in trough FEV_1 at week 12 compared to its components (0.243 [95% CI, 0.202 to 0.284]; $P < 0.001$) compared to placebo (Table 22).

TABLE 20: KEY EFFICACY OUTCOMES: UMECLIDINIUM/VILANTEROL FIXED-DOSE COMBINATION VERSUS PLACEBO, UMECLIDINIUM AND VILANTEROL MONOTHERAPY — INTENTION-TO-TREAT POPULATION

Outcome[a]	DB2113373			
	PLACEBO N = 280	UMEC N = 418	VI N = 421	UMEC/VI FDC N = 413
***Deaths,* n (%)[b]**	0	1 (< 1)	3 (< 1)	3 (< 1)
Health Care Resource Utilization,[c] n (%)				
Hospitalization	9 (3.2)	14 (3.3)	17 (4.0)	13 (3.1)
Emergency room visit	15 (5.4)	18 (2.9)	17 (4.0)	8 (1.9)
On-treatment COPD Exacerbation, n (%)[d]				
Number of patients	35 (12.5)	33 (7.9)	39 (9.3)	27 (6.5)
Withdrawn due to COPD exacerbation[f]	34 (12)	33 (7.9)	38 (9.0)	25 (6.1)
HRQoL: SGRQ Total Score				
LS mean (SE) day 168	46.62 (0.950)	41.93 (0.753)	41.43 (0.760)	41.11 (0.749)
LS mean change (SE) from baseline	–2.56 (0.950)	–7.25 (0.753)	–7.75 (0.760)	–8.07 (0.749)
LS MD (UMEC/VI vs. comparator [95% CI])	–5.51 (–7.88, –3.13)	–0.82 (–2.90, 1.27)	–0.32 (–2.41, 1.78)	-
P value	< 0.001	0.441	0.767	-
Trough FEV_1 (Litres), Week 24				
LS mean (SE)	1.239 (0.0158)	1.354 (0.0126)	1.311 (0.0127)	1.406 (0.0126)
LS mean change (SE) from baseline	0.004 (0.0158)	0.119 (0.0126)	0.076 (0.0127)	0.171 (0.0126)
LS MD (95% CI) (UMEC/VI vs. comparator)	0.167 (0.128 to 0.207)	0.052 (0.017 to 0.087)	0.095 (0.060 to 0.130)	
P value	< 0.001	0.004	< 0.001	
Dyspnea: TDI Focal Score				
LS mean (SE)	1.2 (0.20)	2.2 (0.16)	2.1 (0.15)	2.4 (0.16)
LS MD (95% CI) (UMEC/VI vs. comparator)	1.2 (0.7 to 1.7)	0.3 (-0.2 to 0.7)	0.4 (-0.1 to 0.8)	-
P value	< 0.001	0.244	0.117	-
OR (95% CI) (UMEC/VI vs. comparator)	2.0 (1.5 to 2.8)	1.2 (0.9 to 1.6)	1.4 (1.0 to 1.8)	-
P value	< 0.001	0.143	0.038	-
Rescue SALB use, Weeks 1 to 24				
LS mean (SE)	4.1 (0.20)	3.8 (0.16)	3.2 (0.16)	3.3 (0.16)
LS mean change (SE) from baseline	–1.4 (0.20)	–1.7 (0.16)	–2.4 (0.16)	–2.3 (0.16)
LS MD (95% CI) (UMEC/VI vs.	–0.8 (–1.3 to –	–0.6 (–1.0 to –	0.1 (–0.3 to	-

Outcome[a]	DB2113373			
	PLACEBO N = 280	UMEC N = 418	VI N = 421	UMEC/VI FDC N = 413
comparator)	0.3)	0.1)	0.5)	
P value	0.001	0.014	0.675	-

CDR = CADTH Common Drug Review; CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second; FDC = fixed-dose combination; HRQoL = health-related quality of life; LS = least squares; MD = mean difference; n = number of patients with event; N = number of patients; OR = odds ratio; *P* = probability; SALB = salbutamol; SE = standard error; SGRQ = St. George's Respiratory Questionnaire; TDI = Treatment Dyspnea Index; UMEC = umeclidinium; UMEC/VI = umeclidinium/vilanterol; VI = vilanterol; vs. = versus.
Note: ANCOVA model with covariates of treatment, baseline, smoking status, and centre group.
[a] Refer to Table 11 for baseline data on reported outcomes.
[b] For this review, mortality (death) is considered an efficacy outcome.
[c] In the study, the denominator to calculate the percentage of patients with emergency room and hospital admissions was based on the total patients with health care provider contact during treatment. CDR used the total number of patients in a treatment group as the denominator.
[d] In the study, percentages of patients withdrawing due to COPD exacerbation were calculated using the number of COPD exacerbations as the denominator. CDR used the total number of patients in a treatment group as the denominator.
Source: Clinical Study Report for DB2113373.[9]

TABLE 21: KEY EFFICACY OUTCOMES: UMECLIDINIUM/VILANTEROL FIXED-DOSE COMBINATION VERSUS TIOTROPIUM MONOTHERAPY — INTENTION-TO-TREAT POPULATION

Outcome[a]	DB2113360			DB2113374		ZEP117115	
	VI 25 mcg N = 205	UMEC/ VI FDC N = 207	TIO 18 mcg N = 203	UMEC/VI FDC N = 217	TIO 18 mcg N = 215	UMEC/ VI FDC N = 454	TIO 18 mcg N = 451
***Deaths,* n (%)[b]**	1 (< 1)	1 (< 1)	0	1 (< 1)	2 (< 1)	2 (< 1)	5 (1)
Health Care Resource Utilization,[c] n (%)							
Hospitalization	9 (4.4)	1 (0.5)	3 (1.5)	11 (5.1)	6 (2.8)	2 (4.4)	5 (1)
Emergency room visit	7 (3.4)	5 (2.4)	5 (2.5)	10 (4.6)	6 (2.8)	2 (4.4)	4 (1.0)
On-treatment Exacerbation, n (%)[d]							
Number of patients	17 (8.3)	14 (6.8)	11 (5.4)	26 (12.0)	14 (6.5)	16 (3.5)	29 (6.4)
Withdrawn due to COPD exacerbation	16 (7.8)	13 (6.3)	10 (4.9)	24 (11)	12 (5.6)	16 (3.5)	29 (6.4)
HRQoL: SGRQ Total Score							
LS mean (SE) day 168	41.48 (1.058)	42.90 (1.017)	42.15 (1.054)	39.17 (0.981)	39.34 (0.954)	41.35 (0.538)	43.45 (0.548)
LS mean change (SE) from baseline day 168	–8.29 (1.06)	–6.87 (1.02)	–7.62 (1.05)	–9.95 (0.98)	–9.78 (0.95)	–7.27 (0.538)	–5.17 (0.548)
LS MD (95% CI), (UMEC/VI vs. comparator)	1.42 (–1.46 to 4.30)	-	0.75 (–2.12 to 3.63)	-	–0.17 (–2.85 to 2.52)	-	–2.10 (–3.61 to –0.59)
P value	0.334	-	0.607	-	0.904	-	0.006
HRQoL: EQ-5D Index Score							
Mean (SD)	0.03 (0.164)	0.07 (0.203)	0.04 (0.218)	0.08 (0.215)	0.08 (0.224)	NR	NR

Outcome[a]	DB2113360			DB2113374		ZEP117115	
	VI 25 mcg N = 205	UMEC/ VI FDC N = 207	TIO 18 mcg N = 203	UMEC/VI FDC N = 217	TIO 18 mcg N = 215	UMEC/ VI FDC N = 454	TIO 18 mcg N = 451
Trough FEV_1 (Litres), Week 24							
LS mean (SE)	1.431 (0.0189)	1.521 (0.0183)	1.431 (0.0186)	1.355 (0.0180)	1.295 (0.0176)	1.457 (0.0114)	1.345 (0.0115)
LS mean change (SE) from baseline	0.121 (0.019)	0.211 (0.018)	0.121 (0.019)	0.208 (0.018)	0.149 (0.018)	0.205 (0.0114)	0.093 (0.0115)
LS MD (95% CI), (UMEC/VI vs. comparator)	0.090 (0.039 to 0.142)	-	0.090 (0.039 to 0.141)	-	0.060 (0.010 to 0.109)	-	0.112 (0.081 to 0.144)
P value	< 0.001	-	< 0.001	-	0.0182	-	< 0.001
Dyspnea: TDI Focal Score							
LS Mean (SE) day 168	2.1 (0.2)	2.3 (0.2)	2.4 (0.2)	2.3 (0.3)	2.1 (0.2)	NR	NR
LS MD (95% CI), (UMEC/VI vs. comparator)	0.2 (–0.4 to 0.8)	-	–0.1 (–0.7, 0.5)	-	0.2 (–0.5, 0.9)	NR	NR
P value	0.49	-	0.72	-	0.55	NR	NR
Rescue SALB Use, Weeks 1 to 24							
LS mean (SE)	2.8 (0.21)	2.5 (0.20)	3.2 (0.21)	2.9 (0.23)	3.5 (0.22)	1.8 (0.09)	2.3 (0.09)
LS mean change (SE) from baseline	–1.8 (0.2)	–2.0 (0.2)	–1.4 (0.2)	–2.7 (0.23)	–2.1 (0.22)	–1.3 (0.09)	–0.8 (0.09)
LS MD (95% CI) (UMEC/VI vs. comparator	–0.3 (–0.8 to 0.3)	-	–0.7 (–1.2 to –0.1)	-	0.6 (–1.2 to 0.0)	-	–0.5 (–0.7 to –0.2)
P value	0.39	-	0.022	-	0.07	-	< 0.001

CDR = CADTH Common Drug Review; CI = confidence interval; COPD = chronic obstructive pulmonary disease; DB = double-blind; EQ-5D = EuroQol 5-Dimensions Questionnaire; FEV_1 = forced expiratory volume in one second; FDC = fixed-dose combination; HRQoL = health-related quality of life; LS = least squares; mcg = microgram; MD = mean difference; n = number of patients with event; N = number of patients; NR = not reported; *P* = probability; SALB = salbutamol; SD = standard deviation; SE = standard error; SGRQ = St. George's Respiratory Questionnaire; TDI = Treatment Dyspnea Index; TIO = tiotropium; UMEC/VI = umeclidinium/vilanterol; VI = vilanterol; vs. = versus.

Note: ANCOVA model with covariates of treatment, baseline, smoking status, and centre group.

[a] Refer to Table 12 for baseline data on reported outcomes.

[b] For this review, mortality (death) is considered an efficacy outcome.

[c] In the study, the denominator to calculate the percentage of patients with emergency room and hospital admissions was based on the total patients with health care provider contact during treatment. CDR used the total number of patients in a treatment group as the denominator. For study ZEP117115, emergency room visits and hospital admissions were reported for on-treatment COPD exacerbations only.

[d] In the study, percentages of patients withdrawing due to COPD exacerbation were calculated using the number of COPD exacerbations as the denominator. CDR used the total number of patients in a treatment group as the denominator.

Source: Clinical Study Reports for DB2113360, DB2113374, and ZEP117115.[6,7,11]

TABLE 22: KEY EFFICACY OUTCOMES: CROSSOVER STUDIES — INTENTION-TO-TREAT POPULATION

Outcome[a]	DB2114417				DB2114418			
	PLACEBO N = 170	UMEC N = 49	VI N = 76	UMEC/VI FDC N = 152	PLACEBO N = 151	UMEC N = 40	VI N = 64	UMEC/VI FDC N = 130
***Deaths,* n (%)[b]**	0	0	0	0	0	0	0	1
Health Care Resource Utilization,[c] n (%)								
Hospitalization	2 (1.2)	0	0	0	2 (1.3)	0	0	0
Emergency room visit	2 (1.2)	0	0	0	1 (< 1)	0	0	0
On-treatment Exacerbation, n (%)[d]								
Number of patients	11 (6.5)	1 (2.0)	4 (5.3)	8 (5.3)	16 (10.6)	0	3 (4.7)	2 (1.5)
Withdrawn due to COPD exacerbation	10 (5.9)	0	4 (5.3)	8 (5.3)	14 (9.3)	0	2 (3.1)	2 (1.5)
Trough FEV_1 (Litres), Week 12								
LS mean (SE)	1.404 (0.0149)	1.491 (0.0264)	1.503 (0.0218)	1.615 (0.0156)	1.277 (0.0156)	1.421 (0.0267)	1.388 (0.0222)	1.520 (0.0156)
LS mean change (SE) from baseline	–0.032 (0.0149)	0.054 (0.0264)	0.067 (0.0218)	0.178 (0.0156)	–0.043 (0.0156)	0.101 (0.0267)	0.069 (0.0222)	0.200 (0.0156)
LS MD (95% CI) UMEC/VI vs. comparator	0.211 (0.172 to 0.249)	0.124 (0.067 to 0.181)	0.111 (0.062 to 0.161)	-	0.243 (0.202 to 0.284)	0.099 (0.04 to 0.157)	0.132 (0.081 to 0.183)	-
P value	< 0.001	< 0.001	< 0.001		< 0.001	< 0.001	< 0.001	-
Exercise Dyspnea Scale (Modified Borg Index), Week 12								
LS mean (SE)	3.67 (0.114)	3.51 (0.208)	4.06 (0.172)	3.62 (0.120)	3.31 (0.114)	2.99 (0.205)	2.94 (0.167)	2.95 (0.117)
LS mean change (SE) from baseline	–0.30 (0.114)	–0.45 (0.208)	0.09 (0.172)	–0.35 (0.120	–0.01 (0.114)	–0.33 (0.205)	–0.37 (0.167)	–0.37 (0.117)
LS MD (95% CI) UMEC/VI vs. comparator	–0.05 (–0.37 to 0.27)	0.11 (–0.36 to 0.57)	–0.44 (–0.85 to –0.04)	-	–0.36 (–0.67 to –0.05)	–0.04 (–0.49 to 0.42)	0.00 (–0.39 to 0.40)	-
P value	0.758	0.656	0.032	-	0.025	0.870	0.982	-
3-hour Post-dose EET(s), Week 12								
LS mean change (SE) from baseline	36.7 (13.17)	63.2 (23.93)	26.7 (19.72)	58.6 (13.82)	0.1 (16.66)	25.1 (30.18)	30.7 (24.79)	69.5 (17.09)
LS MD (95% CI) UMEC/VI vs. comparator	21.9 (–14.2 to 58.0)	–4.6 (–57.6 to 48.4)	31.9 (–14.1 to 77.9)	-	69.4 (24.5 to 114.4)	44.4 (–21.8 to 110.6)	38.8 (–18.9 to 96.5)	-
P value	0.234	0.865	0.174	-	0.003	0.188	0.187	-
Rescue SALB use, Week 1 to 12								
LS mean (SE)	2.4 (0.11)	2.2 (0.19)	2.1 (0.16)	1.8 (0.12)	3.0 (0.14)	2.3 (0.25)	2.3 (0.20)	1.8 (0.14)

Outcome[a]	DB2114417				DB2114418			
	PLACEBO N = 170	UMEC N = 49	VI N = 76	UMEC/VI FDC N = 152	PLACEBO N = 151	UMEC N = 40	VI N = 64	UMEC/VI FDC N = 130
LS mean change (SE) from baseline	–0.4 (0.11)	–0.6 (0.19)	–0.7 (0.16)	–1.0 (0.12)	–0.3 (0.14)	–1.0 (0.25)	–1.0 (0.20)	–1.4 (0.14)
LS MD (95% CI) (UMEC/VI vs. comparator	–0.6 (–0.8 to –0.3)	–0.4 (–0.7 to 0.0)	–0.2 (–0.6 to 0.1)	-	–1.2 (–1.5 to –0.8)	–0.4 (–1.0 to 0.1)	–0.4 (–0.9 to 0.0)	-
P value	< 0.001	0.074	0.162	-	< 0.001	0.099	0.068	-

CDR = CADTH Common Drug Review; CI = confidence interval; COPD = chronic obstructive pulmonary disease; DB = double-blind; EET = exercise endurance time; FEV_1 = forced expiratory volume in one second; FDC = fixed-dose combination; LS = least squares; MD = mean difference; n = number of patients with event; N = number of patients; *P* = probability; SALB = salbutamol; SE = standard error; UMEC = umeclidinium; UMEC/VI = umeclidinium/vilanterol; VI = vilanterol; vs. = versus.
Note: ANCOVA model with covariates of treatment, baseline, smoking status, and centre group.
[a] Refer to Table 13 for baseline data on reported outcomes.
[b] For this review, mortality (death) is considered an efficacy outcome.
[c] In the studies, only health care resource utilization upon on-treatment COPD exacerbation was reported. CDR used the total number of patients in a treatment group as the denominator to calculate percentages.
[d] In these studies, COPD exacerbations were considered under lack of efficacy, not adverse events.
Source: Clinical Study Reports for DB2114417 and DB2114418.[8,10]

3.6.7 Other Efficacy Outcomes

a) Adherence

The mean treatment compliance was high across all studies ranging from 97.8% to 101%. For each study, compliance was generally similar among treatment groups.

b) Use of Rescue Medications

The use of salbutamol as a rescue medication generally decreased from baseline in treatment groups across all studies (Table 20, Table 21, Table 22).

In the four parallel-group studies (DB2113373, DB2113360, DB2113374, and ZEP117115), nearly half (range: 43% to 55%) of the patients reported use of a concomitant on-treatment COPD medication not administered for an exacerbation (Table 17, Table 18). The proportion of patients in the exercise tolerance studies (DB2114417 and DB2114418) who reported use of a concomitant on-treatment COPD medication not administered for an exacerbation was generally lower (range: 22% to 45%; Table 19). This is probably because generally, the patients involved in these exercise studies had less severe COPD conditions than those in the other studies. The most common class of concomitant on-treatment COPD medications was inhaled corticosteroids.

c) Days of Missed Work or School

There was no data found in the included studies on the number work or school of days missed as a result of COPD.

3.7 Harms

Only those harms identified in the review protocol are reported below.

3.7.1 Adverse Events

In study DB2113373, AEs were reported in 51% of patients in the UMEC/VI group compared with 46%, 52%, and 48% among patients in the placebo, UMEC 62.5 mcg, and VI 25 mcg monotherapy groups, respectively (Table 23). For studies DB2113360, DB2113374, and ZEP117115, reported AEs in the UMEC/VI groups were 51%, 59%, and 44%, respectively, compared with 39%, 59%, and 42% in the TIO group, in that order (Table 24). In the crossover studies (DB2114417 and DB2114418), proportions of AEs in the UMEC/VI groups were 23% and 44%, respectively, compared with 27% and 39% in the respective placebo groups (Table 25). Infections were the most common AEs, ranging from 6% to 25% across studies. Nasopharyngitis was the single most common infection in all the studies (range: 2% to 10%; Table 23, Table 24, and Table 25).

3.7.2 Serious Adverse Events

The frequency of SAEs was generally low across all the studies. In study DB2113373, SAEs ranged between 3% and 6%, with the UMEC/VI group having 5% of SAEs (Table 23). In studies DB2113360, DB2113374, and ZEP117115, UMEC/VI groups had 3%, 10%, and 4% SAEs, respectively, compared with 6%, 4%, and 4% for the TIO groups in the respective studies (Table 24). Proportions of reported SAEs in studies DB2114417 and DB2114418 were 3% and 2% respectively, compared with 4% and 3% in the placebo groups, respectively (Table 25). In study DB2113373, COPD was reported as SAE by ≥ 1% of patients in all treatment groups with the UMEC/VI group having a 2% rate compared with 1% in the placebo group (Table 23). In studies DB2113360 and DB2113374, COPD reported as SAE in the UMEC/VI groups were 2% and 3%, respectively, compared with 1% and < 1% in the respective TIO groups (Table 24). No other SAE was reported by ≥ 1% of patients in any of the treatment groups. In studies ZEP117115, DB2114417, and DB2114418, there was no SAE reported by ≥ 1% of patients in any of the treatment groups (Table 24, Table 25).

3.7.3 Withdrawals Due to Adverse Events

In study DB2113373, 5% of patients in the UMEC/VI group were withdrawn due to AEs compared with 3%, 7%, and 6% in the placebo, UMEC 62.5 mcg, and VI 25 mcg groups, respectively (Table 23). Proportions of patients withdrawn from studies DB2113360, DB2113374, and ZEP117115 due to AEs ranged from 3% to 9% (Table 24). COPD was the most common AE leading to withdrawal in all four studies (Table 23, Table 24). In studies DB2114417 and DB2114418, WDAEs ranged from 3% to 7%. Dyspnea was the most common cause of WDAEs in both studies (Table 25). In each study, the proportion of patients withdrawn due to COPD was identical to COPD reported as SAE in the study (see Table 23, Table 24, and Table 25 for more details).

3.7.4 Notable Harms

In study DB2113373 cardiovascular disorders were the most common notable harm reported, ranging from 7% to 10%, followed by anticholinergic syndrome (range: 2% to 4%) and pneumonia (up to 2%; see Table 23 for details). Arrhythmias were the most common cardiovascular disorders (range: 2% to 5%). Similar trends of notable harms were observed in studies DB2113360, DB2113374, and ZEP117115 (Table 24). [redacted] (Table 25).

TABLE 23: SUMMARY OF HARMS OUTCOMES: UMECLIDINIUM/VILANTEROL FIXED-DOSE COMBINATION VERSUS PLACEBO, UMECLIDINIUM AND VILANTEROL MONOTHERAPY — INTENTION-TO-TREAT POPULATION

	DB2113373			
	PLACEBO N = 280	**UMEC N = 418**	**VI N = 421**	**UMEC/VI FDC N = 413**
AEs				
Any AEs on-treatment,[a] n (%)	130 (46)	216 (52)	204 (48)	212 (51)
Most common[b]				
Nasopharyngitis	16 (6)	29 (7)	26 (6)	39 (9)
URTI	14 (5)	21 (5)	18 (4)	13 (3)
Headache	26 (9)	32 (8)	25 (6)	35 (8)
Cough	7 (3)	16 (4)	15 (4)	6 (1)
COPD	3 (1)	12 (3)	8 (2)	7 (2)
SAEs, n (%)				
Any SAE on-treatment[a]	9 (3)	27 (6)	24 (6)	21 (5)
Most common[c]				
COPD	3 (1)	12 (3)	8 (2)	7 (2)
WDAEs, n (%)				
Most common[c]				
Any events	9 (3)	31 (7)	24 (6)	22 (5)
COPD	3 (1)	11 (3)	8 (2)	7 (2)
Notable Harms				
Cardiovascular, n (%)	26 (9)	41 (10)	31 (7)	33 (8)
Arrhythmias	12 (4)	20 (5)	18 (4)	8 (2)
Hypertension	6 (2)	12 (3)	7 (2)	15 (4)
Ischemia	3 (1)	7 (2)	3 (< 1)	7 (2)
Anticholinergic syndrome, n (%)	8 (3)	18 (4)	14 (3)	10 (2)
Dizziness	4 (1)	3 (< 1)	3 (< 1)	6 (1)
Dry mouth	1 (< 1)	3 (< 1)	3 (< 1)	0
Urinary retention	0	0	0	0
Vision blurred	1 (< 1)	1 (< 1)	0	0
Pneumonia	2 (< 1)	6 (1)	4 (< 1)	8 (2)

AEs = adverse events; COPD = chronic obstructive pulmonary disease; DB = double=-blind; FDC = fixed-dose combination; n = number of patients with event; N = number of patients; SAEs = serious adverse events; UMEC = umeclidinium; UMEC/VI = umeclidinium/vilanterol; URTI = upper respiratory tract infection; VI = vilanterol; WDAEs = withdrawals due to adverse events.

[a] On-treatment AEs were defined as those occurring with an onset on or after the date of the first dose of study drug, and up to one day after the date of the last recorded dose of study drug.

[b] Reported by ≥ 3% of patients within any treatment group.

[c] Reported by ≥ 1% of patients within any treatment group.

Source: Clinical Study Report for DB2113373.[9]

TABLE 24: SUMMARY OF HARMS OUTCOMES: UMECLIDINIUM/VILANTEROL FIXED-DOSE COMBINATION VERSUS TIOTROPIUM MONOTHERAPY — INTENTION-TO-TREAT POPULATION

	DB2113360			DB2113374		ZEP117115	
	VI 25 mcg N = 205	UMEC/ VI FDC N = 207	TIO 18 mcg N = 203	UMEC/ VI FDC N = 217	TIO 18 mcg N = 215	UMEC/ VI FDC N = 454	TIO 18 mcg N = 451
AEs							
Any AEs on-treatment,[a] n (%)	99 (47)	108 (51)	82 (39)	127 (59)	126 (59)	202 (44)	190 (42)
Most common[b]							
Headache	21 (10)	20 (9)	9 (4)	21 (10)	15 (7)	40 (9)	31 (7)
Nasopharyngitis	17 (8)	21 (10)	16 (8)	14 (6)	17 (8)	28 (6)	30 (7)
URTI	5 (2)	8 (4)	8 (4)	6 (3)	14 (7)	3 (< 1)	4 (< 1)
Cough	4 (2)	7 (3)	5 (2)	5 (2)	6 (3)	13 (3)	15 (3)
SAEs							
Any SAEs on-treatment,[a] n (%)	15 (7)	7 (3)	13 (6)	22 (10)	9 (4)	16 (4)	17 (4)
Most common[c]							
COPD	2 (< 1)	5 (2)	3 (1)	7 (3)	1 (< 1)	[redacted]	[redacted]
WDAEs,[b] n (%)							
Any events	10 (5)	8 (4)	9 (4)	20 (9)	11 (5)	18 (4)	14 (3)
Most common[c]							
COPD	2 (< 1)	5 (2)	3 (1)	7 (3)	1 (< 1)	[redacted]	[redacted]
Pneumonia	1 (< 1)	0	2 (< 1)	2 (< 1)	3 (1)	[redacted]	[redacted]
LRTI	0	0	1 (< 1)	3 (1)	0	[redacted]	[redacted]
Notable Harms							
Cardiovascular, n (%)	21 (10)	24 (11)	9 (4)	13 (6)	18 (8)	9 (2)	7 (2)
Arrhythmias	9 (4)	12 (6)	4 (2)	4 (2)	5 (2)	3 (< 1)	4 (< 1)
Hypertension	8 (4)	8 (4)	3 (1)	2 (< 1)	8 (4)	[redacted]	[redacted]
Ischemia	2 (< 1)	1 (< 1)	3 (1)	3 (1)	1 (< 1)	2 (< 1)	3 (< 1)
Anticholinergic syndrome, n (%)	5 (2)	7 (3)	6 (3)	8 (4)	9 (4)	NR	NR
Dizziness	0	1 (< 1)	0	3 (1)	2 (< 1)	[redacted]	[redacted]
Dry mouth	1 (< 1)	2 (< 1)	3 (1)	2 (< 1)	4 (2)	[redacted]	[redacted]
Urinary retention	0	0	0	1 (< 1)	1 (< 1)	[redacted]	[redacted]
Vision blurred	2 (< 1)	0	0	1 (< 1)	0	[redacted]	[redacted]
Pneumonia	3 (1)	0	7 (3)	3 (1)	3 (1)	[redacted]	[redacted]

AEs = adverse events; COPD = chronic obstructive pulmonary disease; DB = double-blind; FDC = fixed-dose combination; LRTI = lower respiratory tract infection; mcg = microgram; n = number of patients with event; N = number of patients; NR = not rated; SAEs = serious adverse events; TIO = tiotropium; UMEC/VI = umeclidinium/vilanterol; URTI = upper respiratory tract infection; VI = vilanterol; WDAEs = withdrawals due to adverse event.

[a] On-treatment AEs were defined as those occurring with an onset on or after the date of the first dose of study drug, and up to one day after the date of the last recorded dose of study drug.

[b] Reported by ≥ 3% of patients within any treatment group.

[c] Reported by ≥ 1% of patients within any treatment group.

Source: Clinical Study Reports for DB2113360, DB2113374, and ZEP117115.[6,7,11]

TABLE 25: SUMMARY OF HARMS OUTCOMES: CROSSOVER STUDIES — INTENTION-TO-TREAT POPULATION

Outcome	DB2114417				DB2114418			
	PLACEBO N = 170	UMEC N = 49	VI N = 76	UMEC/ VI FDC N = 152	PLACEBO N = 151	UMEC N = 40	VI N = 64	UMEC/ VI FDC N = 130
AEs								
Any AEs on-treatment,[a] n (%)	46 (27)	6 (12)	22 (29)	35 (23)	59 (39)	12 (30)	23 (36)	57 (44)
Most common[b]								
Nasopharyngitis	10 (6)	1 (2)	3 (4)	5 (3)	10 (7)	4 (10)	1 (2)	8 (6)
Headache	7 (4)	0	4 (5)	3 (2)	8 (5)	1 (3)	1 (2)	3 (2)
Cough	2 (1)	0	0	1 (< 1)	3 (2)	0	2 (3)	2 (2)
SAEs								
Any SAEs on-treatment,[a] n (%)	6 (4)	0	7 (9)	4 (3)	4 (3)	1 (3)	2 (3)	3 (2)
Most common[c]								
COPD	1 (< 1)	0	0	0	1 (< 1)	0	0	0
Pneumonia	0	0	1 (1)	0	NR	NR	NR	NR
WDAEs								
Any WDAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Most common[c]								
Dyspnea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COPD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Notable Harms								
Cardiovascular	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arrhythmias	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anticholinergic syndrome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary retention	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AEs = adverse events; COPD = chronic obstructive pulmonary disease; DB = double-blind; FDC = fixed-dose combination; n = number of patients with event; N = number of patients; NR = not rated; SAEs = serious adverse events; UMEC = umeclidinium; UMEC/VI = umeclidinium/vilanterol; VI = vilanterol; WDAEs = withdrawals due to adverse event.

[a] On-treatment AEs and SAEs were defined as those occurring with an onset on or after the date of the first dose of study drug, and up to one day after the date of the last recorded dose of study drug.

[b] Reported by ≥ 3% of patients within any treatment group.

[c] Reported by ≥ 1% of patients within any treatment group, or any COPD or pneumonia.

Source: Clinical Study Reports for DB2114417 and DB2114418.[8,10]

4. DISCUSSION

4.1 Summary of Available Evidence

Six DB, randomized controlled phase 3 studies in patients with moderate to severe COPD met the inclusion criteria of this review. One placebo-controlled study (DB2113373) evaluated the efficacy and safety of UMEC/VI and its components — UMEC 62.5 mcg and VI 25 mcg (as monotherapy) — over 24 weeks. In three other studies (DB2113360, DB2113374, and ZEP117115), the efficacy of UMEC/VI was compared with tiotropium 18 mcg over 24 weeks. Studies DB2114417 and DB2114418 were 12-week crossover studies comparing UMEC/VI, VI 25 mcg, UMEC 62.5 mcg, and placebo. The primary end point of the four parallel treatment studies was the trough FEV_1 on day 169 (week 24), whereas the two crossover studies of UMEC/VI assessed treatment effects on improving exercise endurance over 12 weeks on the co-primary end points of EET and trough FEV_1.

The main limitations of the studies included the fact that all were ≤ 24 weeks in duration, which is not likely a sufficient duration to assess key clinical outcomes such as mortality and mortality due to COPD. Furthermore, none of the studies was designed to evaluate treatment effects on COPD exacerbations. Patients who were hospitalized for COPD within 12 weeks prior to screening, which may have been attributed to a COPD exacerbation, were not included and those who developed exacerbation in the course of the study were withdrawn. Patient groups expressed concern about COPD exacerbation, as this is associated with both short- and long-term consequences on overall health (APPENDIX 1). Therefore, knowing how UMEC/VI resolves or is associated with exacerbation is an important issue. The TIO-controlled trials were reported as double-blinded and double-dummy studies; however, the investigators reported that although the TIO and placebo capsules were closely matched in colour, the blinding of TIO was imperfect because the TIO capsules had trade markings and the placebo capsules did not. Therefore, the DB may have been compromised in these studies. There was a substantial proportion of discontinuations (ranging as high as 20% to 27% in study DB2113373) across studies. Although there was no clear discontinuation differential among groups within studies (except those on placebo more frequently discontinued), there is a concern regarding the validity of the findings once frequencies of discontinuations are this high. Finally, there were no head-to-head studies comparing UMEV/VI with other LABA/LAMA combinations.

4.2 Interpretation of Results

4.2.1 Efficacy

Mortality and morbidity were key outcomes of this review; however, none of the included studies was adequately designed to assess such outcomes. The overall rate of death was ≤ 1% across studies. No deaths were reported in any of the placebo groups regardless of the study. Study ZEP117115 had the most deaths in treatment group of the included studies, with five deaths (1%) in the TIO group (two deaths due to COPD) versus two deaths (< 1%) in the UMEC/VI group (none due to COPD). However, as mentioned, none of the studies was large enough or of sufficient duration to determine whether a difference among treatments in deaths exists. Few studies reported outcomes that might be considered indicators of morbidity, such as hospitalizations. ER visits and intensive care unit stays were rare occurrences and occurred in similar proportions of patients among groups and across studies. Again, these studies were not designed to examine these outcomes and they included largely patients with stable COPD. Therefore, it is not surprising that a difference in health care resource use was not observed. Given the importance of these events to patients and as cost drivers in the health care system, it would have been useful to have a study that was designed to assess these outcomes.

Similarly, exacerbations are another key outcome in COPD of interest in the review, and according to the patient group submission, are an important consideration for COPD patients. However, none of the included studies was designed to assess the comparative effect of UMEC/VI on exacerbation rates.

Quality of life is another important consideration for COPD patients, as noted in the patient input summary. Study DB2113373 showed a statistically and clinically significant (MCID 4 points) improvement in favour of UMEC/VI compared with placebo for HRQoL as measured by reduction in SGRQ total score at week 24. There were no statistically significant differences between UMEC/VI and its individual components for improving SGRQ total score. In the three TIO-controlled studies, differences in SGRQ scores between UMEC/VI and TIO were not statistically significant in studies DB2113360 and DB2113374, while they were statistically significantly different in study ZEP117115 between UMEC/VI and TIO. Therefore, the clinical significance of the observed differences between UMEC/VI and active comparators on HRQoL is not clear.

Improving lung function in and of itself (as measured using pulmonary function tests) is not an objective of COPD management,[30-32] but it is the primary end point most frequently used in trials on drugs to treat COPD and is accepted by regulatory agencies in interpreting drug efficacy in COPD trials.[33] UMEC/VI demonstrated statistically and clinically significant improvements in the trough FEV_1 at 12 weeks and 24 weeks compared with placebo. However, because the standard of care for patients with COPD in Canada who are most likely to require combination LABA and LAMA treatment (i.e., those with moderate to severe COPD with persistent dyspnea despite LABA or LAMA monotherapy[2]) is not as-needed salbutamol, the relevance of improvements in FEV_1 versus placebo is somewhat uncertain. UMEC/VI also demonstrated statistically significant improvements in trough FEV_1 at 12 weeks and 24 weeks compared with its individual components and TIO. However, the clinical relevance of these differences is also somewhat difficult to judge given that in most cases, the change in trough FEV_1 from baseline for the active comparators met or exceeded the within-group MCID of 0.1 L, making it less likely to observe a clinically important difference among groups. However, it may be unrealistic to expect the incremental improvement in trough FEV_1 gained by adding a second drug to a first to be as great as the difference between an active and placebo, or to expect the improvement between two actives to meet or exceed the MCID.[30]

Treatment with UMEC/VI resulted in statistically significant improvements in dyspnea as measured by TDI scores, and more responders achieved the MCID of ≥ 1 unit improvement at week 24 compared with placebo in study DB2113373. However, there were no statistically significant differences between UMEC/VI and TIO in the two TIO-controlled studies that assessed dyspnea as measured by the TDI. Although there was no statistically significant difference between UMEC/VI and TIO with respect to effects on dyspnea, this does not indicate equivalence or similarity of effect between these drugs for this outcome.

Exercise tolerance was evaluated in two crossover RCTs. As in the other studies, the analysis followed a step-down hierarchy such that unless a comparison that was higher in order demonstrated statistical significance, inference about statistical significance could not be made from a lower order comparison. In study DB2114417, comparison of the post-dose EET at week 12 between UMEC/VI 125 mcg/25 mcg and placebo that was first in the hierarchy did not reach statistically significant difference. Failure of the hierarchical testing prevented inferences of statistical significance from other comparisons to be made. For the co-primary outcomes, compared with placebo, treatment with UMEC/VI achieved a modest improvement in post-dose EET (21.9 seconds versus the clinically meaningful difference of 45 seconds to 85 seconds), while trough FEV_1 at 12 weeks showed a clinically relevant improvement of 0.211 L

compared with placebo. In the other exercise endurance study (DB2114418), UMEC/VI treatment demonstrated statistically significant and clinically meaningful improvement in EET compared with placebo, but not versus its components administered individually. Treatment with UMEC/VI also achieved statistically and clinically significant improvements in trough FEV_1 at week 12 compared with placebo and versus its components administered individually. Considering that the two studies shared similarity in methodology and patients' baseline characteristics, it is not clear why study DB2114418 with a smaller sample size (N = 308) showed statistically significant difference while DB2114417 (N = 349) did not.

A potential advantage of UMEC/VI is the administration of a LABA/LAMA together once daily for patients requiring dual administration of a LABA and a LAMA. A once-daily dosing regimen might lead to improved compliance versus a twice-daily regimen. The mean treatment compliance was high across all studies ranging from 97.8% to 101%. For each study, compliance was generally similar between treatment groups. Compliance is typically high in clinical trials, as patients are more closely monitored and tend to be a more motivated population. As well, the studies did not describe patients as having received some type of training on use of the inhaler devices. Moreover, it was not clear whether patients actually demonstrated that they knew how to use the devices before initiating therapy. Although compliance was high in the included studies, this simply reflects the number of doses actuated rather than whether the dose was delivered optimally.

The included studies did not address the potential use of UMEC/VI as part of triple therapy with an ICS. Triple therapy is recommended as part of the COPD management guidelines for patients with moderate to severe disease and persistent symptoms.[5] Across the studies included in this review, between 40% and 50% of patients were classed as having severe disease at baseline. It would seem that triple therapy would be appropriate for at least some of these patients who had a history of exacerbation, particularly those who did not respond to dual therapy. If these patients are determined to be treatment failures, they might then be switched to triple therapy, with an added cost to the health care system and risk of harm for the patient. However, the role of UMEC/VI in triple therapy regimens has yet to be established.

As mentioned, a key limitation of the included studies is the lack of a head-to-head comparison with another LABA/LAMA combination inhaler. Indacaterol plus glycopyrronium (Ultibro Breezhaler) is the other LABA/LAMA combination product approved for treating COPD in Canada. As well, RCTs have been conducted on other non–fixed-dose LABA/LAMA combinations such as indacaterol plus tiotropium and formoterol plus tiotropium (APPENDIX 7). Given the lack of head-to-head comparisons, the manufacturer provided an indirect comparison that has been summarized and critically appraised in APPENDIX 7. Using the Bucher method of indirect comparison, the manufacturer's analysis indicated no differences between UMEC/VI versus indacaterol plus tiotropium, indacaterol plus glycopyrronium, or fluticasone/salmeterol plus tiotropium with respect to change in trough FEV_1, HRQoL (assessed using SGRQ), rescue medication use, and dyspnea (assessed using TDI) at 12-week and 24-week time points. However, the findings from the indirect comparison should be interpreted with considerable caution given numerous important limitations of the analysis, largely related to poor reporting of methods used, the characteristics of the included studies, and the lack of comparisons related to key outcomes such as exacerbations, exercise tolerance, and AEs.

4.2.2 Harms

Across studies, the overall incidence of on-treatment AEs among treatment groups was generally similar. In the placebo-controlled studies, UMEC/VI consistently had higher rates of AEs than placebo. In one of the TIO-controlled studies (DB2113360), the overall incidence of AEs was lower in the TIO

treatment group (39%) compared with the UMEC/VI (51%). In another TIO-controlled study (DB2113374), the overall incidence of AEs was identical for both UMEC/VI and TIO treatment groups (59% in both cases), while a third TIO-controlled study (ZEP117115) demonstrated similar but different overall incidence rates for the UMEC/VI (44%) and the TIO (42%) treatment groups. The overall incidence of on-treatment AEs for UMEC/VI in one of the exercise endurance studies (DB2114417) was lower (23%) compared with the overall incidence of on-treatment AEs (44%) of the same drug in the other exercise study (DB2114418), which had similar methodology and a smaller sample size.

Notable harms were considered based on the anticholinergic and beta2-agonist components of UMEC/VI. Anticholinergic or muscarinic antagonists are known to be associated with cardiovascular AEs. Cardiovascular AEs were generally low with overall incidences ranging from 1% to 11%. Incidences of anticholinergic syndrome (including dry mouth, dizziness, urinary retention, worsening vision) were also low and with similarities across treatment groups when they occurred. Pneumonia is another key safety issue associated with COPD and COPD management. Patients with COPD are at higher risk of pneumonia and this risk increases further with use of ICS. As it does not contain a corticosteroid, UMEC/VI might be expected to carry a lower risk of pneumonia than ICS/LABA combinations. Overall, the number of events of pneumonia was low across studies (typically about 1% of patients). However, given the small number of events related to pneumonia, cardiovascular, and anticholinergic effects, it cannot be ascertained whether UMEC/VI does have a lower risk of these versus comparators. A larger, longer-term study might be able to determine whether such a difference exists for UMEC/VI versus comparators.

Another safety issue relevant to the UMEC/VI combination is the increased risk of death with LABAs. This risk has been associated with use of LABA for asthma, particularly when used as monotherapy, and is noted in the product monograph for UMEC/VI.[16] Although this safety warning has not been extended to COPD, there are a number of patients with COPD who exhibit airway reversibility suggestive of underlying asthma. There was no evidence from the included trials of an increased risk of sudden death due to asthma with the use of UMEC/VI; however, given that patients may be at higher risk with longer-term use of LABAs, these studies may not be of sufficient duration or sample size to assess this risk.

5. CONCLUSIONS

Six DB RCTs met the inclusion criteria for this review, three of which compared UMEC/VI with its components administered as monotherapies, as well as placebo, and another three studies compared UMEC/VI with tiotropium monotherapy. Two studies were 12-week crossover studies designed to assess effects on exercise tolerance and trough FEV_1 at 12 weeks, while the remaining studies were parallel designs that assessed effects on change in trough FEV_1 at week 24. None of the studies was designed to evaluate the comparative treatment effects of UMEC/VI on mortality and morbidity (e.g., hospitalizations and exacerbations), which were key outcomes for the review and identified by patient groups as important to them.

A statistically significant improvement in HRQoL (on the St. George's Respiratory Questionnaire) with UMEC/VI was found in only one study versus tiotropium and one study versus placebo. Treatment with UMEC/VI resulted in statistically significant improvements in trough FEV_1 at week 24 versus placebo and active comparators in each of the studies. However, the clinical relevance of the effects of UMEC/VI versus its individual components and TIO is somewhat difficult to judge given that in most cases the change in trough FEV_1 from baseline for the active comparators met or exceeded the within-group MCID of 0.1 L, making it less likely to observe a clinically important difference among groups. Hence, the

clinical importance of the incremental gain in FEV_1 improvement with the combination of UMEC/VI versus a single long-acting bronchodilator is difficult to determine. Improvements in dyspnea (TDI score assessed in three studies) were in favour of UMEC/VI versus placebo in one study, but not versus TIO in two studies. Furthermore, only one of the two exercise endurance studies demonstrated a statistically and clinically significant improvement in the co-primary efficacy end points of post-dose EET and trough FEV_1 at week 12 in favour of UMEC/VI compared with placebo.

The manufacturer provided an indirect comparison that suggested no difference between UMEC/VI and other LABA/LAMA combinations with respect to change in trough FEV_1, HRQoL, rescue medication use, and dyspnea at 12 week and 24 week time points. However, the findings from the indirect comparison should be interpreted with considerable caution given numerous important limitations of the analysis, largely related to poor reporting of methods used, the characteristics of the included studies, lack of head-to-head comparisons, and the lack of comparisons related to key outcomes such as exacerbations, exercise tolerance, and AEs.

The most common AEs with UMEC/VI were nasopharyngitis and headache. No clear association with the occurrence of cardiovascular, anticholinergic, or pneumonia events could be determined because events occurred infrequently and the studies were only 12 weeks to 24 weeks in duration.

APPENDIX 1: PATIENT INPUT INFORMATION

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

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

COPD Canada is an independent non-profit patient advocacy and education association, established in 2005, with a mandate to assist Canadians who suffer from chronic obstructive pulmonary disease (COPD). It provides materials and services in a variety of formats to patients and their families and also to Canadian medical professionals, government agencies, non-governmental organizations, and other health care personnel. Membership in COPD Canada is restricted to patients with COPD and their families. COPD Canada has received unrestricted educational grants from Almirall Canada, Astra-Zeneca (AZ) Canada, Novartis Pharmaceuticals and Nycomed/Takeda; educational grants from ProResp Canada; and a general grant from GlaxoSmithKline (GSK) Canada. It declared no conflict of interest in the preparation of this submission.

The Ontario Lung Association (OLA) is a registered charity that both assists and empowers patients and caregivers of those living with lung disease. OLA provides both programs and services to patients and health care providers, campaigns for lung health improvement, and also invests in lung research. The OLA has received both sponsorships and grants from Rx&D and the following pharmaceutical companies: Pfizer, GSK, Boehringer Ingelheim, AZ, Merck, Novartis, Takeda, InterMune, Grifols, Actelion, Astellas, Bayer, J&J, OHRSA, Roche, Valeant Pharmaceuticals, and Eli Lilly. It declared no conflict of interest in preparation of this submission.

The New Brunswick Lung Association (NBLA) is a provincial member of the Canadian Lung Association, which delivers community health programs and provides support for and coordination of respiratory health research. NBLA receives funding for a Health Symposium and patient counselling from: Takeda, AstraZeneca, Boehringer Ingelheim, Merck, Pfizer, GlaxoSmithKline, and Actelion. NBLA declared no conflicts of interest in the preparation of this submission.

2. Condition and Current Therapy-related Information

The patient groups gathered this information through conversations with patients and caregivers by phone or in group pulmonary rehabilitation settings, information from a certified respiratory educator, patient surveys, the personal experiences of members and published scientific literature, and from the BreathWorks helpline.

COPD is a disease associated with considerable burdens on patients, their families, and the health care system. It is characterized by shortness of breath, difficulty breathing, coughing, fatigue, low energy, mucus, wheezing, and exacerbations. Everyday life is affected, including the patient's ability to breathe, talk, sleep, work, and socialize. As the disease progresses, patients need to adapt their lifestyle in order to cope with their condition. This can include early retirement, walking very slowly, avoiding public places with stairs or without washrooms on the ground floor, being vigilant with respect to weather conditions, and using supplemental oxygen when walking, during pulmonary rehabilitation, or while on an aircraft. Ongoing issues such as the loss of appetite, increased risk of infections, chronic bronchitis, increased reliance on supplemental oxygen, and increased risk of hospitalization and mortality are also of concern. Exacerbations are a source of concern for the COPD patient as they are associated with both short- and

long-term consequences on overall health. Furthermore, patients often feel socially isolated, may suffer social stigma, feel a loss of independence, and find their relationships with loved ones are affected, leading to lower emotional well-being and depression.

Caregivers and families, who are often the children and spouses of those with COPD, are also heavily affected by the disease, including having limited time to manage their own health, feelings of isolation, anxiety, stress, depression, fatigue, unending days, increased need for social support, decrease in ability to travel, and decreased independence. Adult children caring for their parents are often torn between caring for their parent and their young families.

There is no cure for COPD, no medications that reverse the loss of lung function caused by COPD, and no drug that has demonstrated effectiveness in halting the progression of the disease. The goals of currently available medications for COPD are to maintain control of symptoms and prevent or minimize the frequency and duration of exacerbations. Non-drug interventions include pulmonary rehabilitation, exercise programs, breathing lessons, and use of supplemental oxygen. The main surgical options include lung transplantation and lung reduction surgery, options that are only available to a small group of COPD patients who qualify.

Treatments tried by those interviewed included Spiriva, Advair, Symbicort, Daxas, prednisone, Ventolin, Atrovent, Serevent, Onbrez, and Breo Ellipta. While current treatments provide some relief, they do have side effects such as palpitations, dry mouth, voice hoarseness, mouth sores, visual and urinary problems, and impact on mood. Rescue medications are used for symptom control, but they do not improve long-term lung function. Exacerbations are often managed with prednisone and antibiotics. While prednisone works quickly, it is associated with numerous side effects.

Patients identified a need for additional medications to improve breathing and lung function. Patients with COPD ranked in the top three for “frequency of reason for call” to the NBLA BreathWorks helpline, with the main reason for the call being to seek information and assistance for poorly managed symptoms.

Accessing current therapies is a notable challenge for the economically disadvantaged and those relying on provincial drug formularies (e.g., patients older than 65 years). While some provinces provide good coverage (e.g., Alberta), there remains large variability in COPD medication coverage among the other provinces (e.g., poor coverage in Atlantic Canada and moderate-to-poor in Ontario).

3. Related Information About the Drug Being Reviewed

No patient experience with Anoro Ellipta was available for this submission.

Patients are looking for agents that can improve lung function and quality of life, reduce exacerbations, reduce fatigue, reduce hospital admissions, and delay disease progression and over the long term improve survival. In addition, therapies that offer a convenient treatment option for COPD patients who require long-term maintenance therapy are desirable.

Patients with COPD believe that Anoro Ellipta will lead to an improvement in overall disease management as it is expected to reduce airflow obstruction, improve breathing, and reduce the need for rescue medication. Inclusion of two bronchodilators in a single inhaler simplifies administration. The once-daily morning treatment should provide relief and let patients get on with their day as well as help with compliance. As a nonsteroidal, Anoro Ellipta is expected to have fewer side effects than the inhaled corticosteroids therapies that are currently being prescribed.

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:	August 26, 2014
Alerts:	Weekly search updates until December 10, 2014
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	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
.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-DATABASE STRATEGY

#	Searches
1	Anoro*.ti,ot,ab,sh,hw,rn,nm.
2	(umeclidinium* or GSK 573719 or GSK573719 or GE2T1418SV or 869113-09-7 or 869185-19-3).ti,ot,ab,sh,hw,rn,nm.
3	(Vilanterol* or GW 642444 or GW-642444x or GW642444x or 028LZY775B or 503070-58-4 or 503068-34-6).ti,ot,ab,sh,hw,rn,nm.

MULTI-DATABASE STRATEGY	
#	**Searches**
4	2 and 3
5	1 or 4
6	5 use pmez
7	umeclidinium plus vilanterol/
8	Anoro*.ti,ab.
9	(umeclidinium* or GSK 573719 or GSK573719 or GE2T1418SV or 869113-09-7 or 869185-19-3).ti,ab.
10	(Vilanterol* or GW 642444 or GW-642444x or GW642444x or 028LZY775B or 503070-58-4 or 503068-34-6).ti,ab.
11	9 and 10
12	7 or 8 or 11
13	12 not conference abstract.pt.
14	13 use oemezd
15	6 or 14

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:	August 2014
Keywords:	Anoro Ellipta (umeclidinium/vilanterol)
Limits:	No date or language limits used

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

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

APPENDIX 3: EXCLUDED STUDIES

There were no excluded studies.

Reference	Reason for Exclusion

APPENDIX 4: DETAILS OF OTHER OUTCOME DATA

TABLE 26: OTHER OUTCOMES: UMECLIDINIUM/VILANTEROL FIXED-DOSE COMBINATION VERSUS PLACEBO, UMECLIDINIUM/VILANTEROL AND VILANTEROL MONOTHERAPY — INTENTION-TO-TREAT POPULATION

Outcome[a]	DB2113373			
	PLACEBO N = 280	UMEC N = 418	VI N = 421	UMEC/VI FDC N = 413
Responders by TDI Focal Score at day 168, N (%)[c]				
Responders, n (%)	106 (41)	207 (53)	197 (51)	226 (58)
Non-responders, n (%)	154 (59)	187 (47)	192 (49)	163 (42)
OR (95% CI) (UMEC/VI vs. comparator	2.0 (1.5 to 2.8)	1.2 (0.9 to 1.6)	1.4 (1.0 to 1.8)	
P value	< 0.001	0.143	0.038	
Responders by SGRQ at day 168, n (%)[d]				
Responders, n (%)	86 (34)	172 (44)	181 (48)	188 (49)
OR (95% CI) (UMEC/VI vs. comparator	2.0 (1.4 to 2.8)	1.2 (0.9 to 1.6)	1.1 (0.8 to 1.4)	-
P value	< 0.001	0.178	0.602	-
Time to First Exacerbation				
Probability of exacerbation, % (95% CI)	13.7 (10.0 to 18.6)	8.9 (6.4 to 12.4)	11.7 (8.1 to 16.8)	9.9 (5.2 to 18.4)
HR (95% CI) (UMEC/VI vs. comparator)	0.5 (0.3 to 0.8)	0.8 (0.5 to 1.3)	0.7 (0.4 to 1.1)	-
P value	0.004	0.391	0.121	
Health Care Resource Utilization				
Number of emergency room visits (total)	3	6	8	3
0 visits, n (%)	278 (> 99)	412 (99)	414 (98)	410 (> 99)
1 visit, n (%)	1 (< 1)	6 (1)	6 (1)	3 (< 1)
2 visits, n (%)	1 (< 1)	0	1 (< 1)	0
Number of days in intensive care (total)	0	1	1	0
0 days, n (%)	280 (100)	417 (> 99)	420 (> 99)	413 (100)
1 day, n (%)	0	1 (< 1)	1 (< 1)	0

AE = adverse event; CI = confidence interval; DB = double-blind; FDC = fixed-dose combination; HR = hazard ratio; n = number of patients with event; N = number of patients; OR = odds ratio; *P* = probability; SGRQ = St. George's Respiratory Questionnaire; TDI = Treatment Dyspnea Index; UMEC = umeclidinium; UMEC/VI = umeclidinium/vilanterol; VI = vilanterol; vs. = versus.
Note: Analysis was performed using a separate logistic regression model at each visit with covariates of treatment, BDI focal score, smoking status, and centre group.
[a] Refer to Table 11 for baseline data on reported outcomes.
[b] For this review, mortality (death) is considered an efficacy outcome.
[c] Response was defined as a TDI focal score of at least 1 unit. Non-response was defined as a TDI focal score of less than 1 unit or a missing TDI focal score with no subsequent non-missing TDI assessments.
[d] Response was defined as a SGRQ total score of 4 units below baseline (score prior to dosing on day 1) or lower. Non-response was defined as a SGRQ total score higher than 4 units below baseline, or a missing change from baseline in SGRQ total score with no subsequent non-missing scores.
[e] In the study, COPD exacerbations were considered under lack of efficacy, not AEs.
Source: Clinical Study Report for DB2113373.[9]

TABLE 27: OTHER OUTCOMES: UMECLIDINIUM/VILANTEROL FIXED-DOSE COMBINATION VERSUS PLACEBO, UMECLIDINIUM/VILANTEROL AND TIOTROPIUM MONOTHERAPY — INTENTION-TO-TREAT POPULATION

Outcome [a]	DB2113360			DB2113374		ZEP117115	
	VI 25 mcg N = 205	UMEC/ VI FDC N = 207	TIO 18 mcg N = 203	UMEC/ VI FDC N = 217	TIO 18 mcg N = 215	UMEC/ VI FDC N = 454	TIO 18 mcg N = 451
Responders by TDI Focal Score at day 168, n (%)[c]	193 (100)	199 (100)	188 (100)	194 (100)	194 (100)	NR	NR
Responders, n (%)	95 (49)	110 (55)	112 (60)	111 (57)	98 (51)	NR	NR
OR (95 % CI), UMEC/VI vs. comparator	1.4 (0.9 to 2.0)	-	0.9 (0.6 to 1.3)	-	1.3 (0.9 to 1.9)	NR	NR
P value	0.155	-	0.464	-	0.198	NR	NR
Responders by SGRQ at day 168, n (%)[d]	186 (100)	193 (100)	178 (100)	190 (100)	190 (100)	454 (100)	430 (100)
Responders, n (%)	97 (52)	94 (49)	92 (52)	103 (54)	104 (55)	237 (53)	196 (46)
OR (95% CI) (UMEC/VI vs. comparator	0.8 (0.6 to 1.3)	-	0.9 (0.6 to 1.3)	-	1.0 (0.6 to 1.5)	-	1.4 (1.0 to 1.8)
P value	0.414	-	0.537	-	0.887		0.022
Time to first exacerbation							
Probability event % (95% CI)	9.0 (5.7 to 14.1)	7.2 (4.3 to 11.9)	10.5 (3.8 to 27.3)	13.4 (9.3 to 19.1)	6.9 (4.2 to 11.4)	3.6 (2.2 to 5.9)	6.7 (4.7 to 9.5)
HR (95% CI)	0.7 (0.4 to 1.5)		1.2 (0.5 to 2.6)	-	1.9 (1.0 to 3.6)		0.5 (0.3 to 1.0)
P value	0.42		0.71	-	0.06		0.044
Health Care Resource Utilization							
Number of ER visits (total)	1	4	2	8	2	NR	NR
0 visits, n (%)	204 (> 99)	203 (98)	201 (> 99)	209 (96)	213 (> 99)	NR	NR
1 visit, n (%)	1 (< 1)	3 (< 1)	2 (< 1)	7 (3)	2 (< 1)	NR	NR
2 visits, n (%)	0	1 (< 1)	0	1 (< 1)	0	NR	NR
Number of days in intensive care (total)	0	0	0	11	0	NR	NR
0 days, n (%)	205 (100)	207 (100)	203 (100)	216 (> 99)	215 (100)	NR	NR
1 day, n (%)	0	0	0	0	0	NR	NR

Outcome [a]	DB2113360			DB2113374		ZEP117115	
	VI 25 mcg N = 205	UMEC/ VI FDC N = 207	TIO 18 mcg N = 203	UMEC/ VI FDC N = 217	TIO 18 mcg N = 215	UMEC/ VI FDC N = 454	TIO 18 mcg N = 451
≥ 3 days, n (%)				1 (< 1)	0	NR	NR

AE= adverse event; CI = confidence interval; DB = double-blind; ER = emergency room; FDC = fixed-dose combination; HR = hazard ratio; mcg = microgram; n = number of patients with event; N = number of patients; NR = not reported; OR = odds ratio; *P* = probability; SGRQ = St. George's Respiratory Questionnaire; TDI = Treatment Dyspnea Index; TIO = tiotropium; UMEC/VI = umeclidinium/vilanterol; VI = vilanterol; vs. = versus.
Note: Analysis was performed using a separate logistic regression model at each visit with covariates of treatment, BDI focal score, smoking status, and centre group.
[a] Refer to Table 12 for baseline data on reported outcomes.
[b] For this review, mortality (death) is considered an efficacy outcome.
[c] Response was defined as a TDI focal score of at least 1 unit. Non-response was defined as a TDI focal score of less than 1 unit or a missing TDI focal score with no subsequent non-missing TDI assessments.
[d] Response was defined as a SGRQ total score of 4 units below baseline (score prior to dosing on day 1) or lower. Non-response was defined as a SGRQ total score higher than 4 units below baseline, or a missing change from baseline in SGRQ total score with no subsequent non-missing scores.
[e] In these studies, COPD exacerbations were considered under lack of efficacy, not AEs.
Source: Clinical Study Reports for DB2113360, DB2113374, and ZEP117115.[6,7,11]

TABLE 28: OTHER OUTCOMES: CROSSOVER STUDIES — INTENTION-TO-TREAT POPULATION

Outcome[a]	DB2114417				DB2114418			
	PLACEBO N = 170	UMEC N = 49	VI N = 76	UMEC/ VI FDC N = 152	PLACEBO N = 151	UMEC N = 40	VI N = 64	UMEC/ VI FDC N = 130
Measures of Hyperinflation/Lung Volume, Week 12								
Trough FRC (L)								
LS mean (SE)	4.752 (0.0494)	4.470 (0.0899)	4.623 (0.0738)	4.513 (0.0523)	4.718 (0.0460)	4.601 (0.0804)	4.583 (0.0666)	4.367 (0.0469)
LS mean change (SE) from baseline	0.020 (0.0494)	0.262 (0.0899)	–0.109 (0.0738)	0.219 (0.0523)	–0.083 (0.0460)	–0.200 (0.0804)	–0.218 (0.0666)	–0.434 (0.0469)
LS MD (95% CI) UMEC/VI vs. comparator	–0.238 (–0.373 to –0.104)	[redacted]	[redacted]	-	–0.351 (–0.473 to –0.230)	[redacted]	[redacted]	-
P value	< 0.001	[redacted]	[redacted]	-	< 0.001	[redacted]	[redacted]	-
Trough RV (L)								
LS mean (SE)	4.053 (0.0521)	3.677 (0.0948)	3.876 (0.0779)	3.758 (0.0552)	3.907 (0.0491)	3.691 (0.0847)	3.666 (0.0705)	3.441 (0.0500)
LS mean change (SE) from baseline	0.039 (0.0521)	–0.337 (0.0948)	–0.138 (0.0779)	–0.255 (0.0552)	–0.049 (0.0491)	–0.266 (0.0847)	–0.291 (0.0705)	–0.516 (0.0500)
LS MD (95% CI) UMEC/VI vs. comparator	–0.295 (–0.436 to –0.154)	[redacted]	[redacted]	-	–0.466 (–0.593 to –0.340)	[redacted]	[redacted]	-
P value	< 0.001	[redacted]	[redacted]	-	< 0.001	[redacted]	[redacted]	-
Trough IC (L)								
LS mean (SE)	2.255 (0.0255)	2.282 (0.0457)	2.324 (0.0377)	2.453 (0.0269)	2.145 (0.0271)	2.243 (0.0471)	2.246 (0.0391)	2.382 (0.0274)
LS mean change (SE) from baseline	–0.002 (0.0255)	0.025 (0.0457)	0.067 (0.0377)	0.196 (0.0269)	–0.021 (0.0271)	0.077 (0.0471)	0.081 (0.0391)	0.216 (0.0274)
LS MD (95% CI) UMEC/VI vs. comparator	0.198 (0.131 to 0.265)	[redacted]	[redacted]	-	0.237 (0.166 to 0.308)	[redacted]	[redacted]	-
P value	< 0.001	[redacted]	[redacted]	-	< 0.001	[redacted]	[redacted]	-
3-hour Post-dose IC, Week 12								
LS mean (SE)	2.285 (0.0259)	2.399 (0.0463)	2.417 (0.0382)	2.524 (0.0274)	2.146 (0.0273)	2.322 (0.0465)	2.323 (0.0389)	2.463 (0.0276)
LS mean change (SE) from baseline	0.028 (0.0259)	0.142 (0.0463)	0.160 (0.0382)	0.267 (0.0274)	–0.021 (0.0273)	0.155 (0.0465)	0.156 (0.0389)	0.295 (0.0276)
LD MD (95% CI) UMEC/VI vs. comparator	0.238 (0.171 to 0.306)	[redacted]	[redacted]	-	0.316 (0.248 to 0.385)	[redacted]	[redacted]	(0.0
P value	< 0.001	[redacted]	[redacted]	-	< 0.001	[redacted]	[redacted]	
3-hour Post-dose FEV_1, Week 12								
LS mean (SE)	1.428	1.556	1.549	1.689	1.301	1.488	1.463	1.617

Outcome[a]	DB2114417				DB2114418			
	PLACEBO N = 170	**UMEC N = 49**	**VI N = 76**	**UMEC/ VI FDC N = 152**	**PLACEBO N = 151**	**UMEC N = 40**	**VI N = 64**	**UMEC/ VI FDC N = 130**
	(0.0159)	(0.0277)	(0.0229)	(0.0166)	(0.0175)	(0.0296)	(0.0246)	(0.0175)
LS mean change (SE) from baseline	–0.007 (0.0159)	0.122 (0.0277)	0.115 (0.0229)	0.254 (0.0166)	–0.019 (0.0175)	0.168 (0.0296)	0.143 (0.0246)	0.297 (0.0175)
LS MD (95% CI) UMEC/VI vs. comparator	0.261 (0.221 to 0.301)	[redacted]	[redacted]	-	0.316 (0.272 to 0.361)	[redacted]	[redacted]	-
P value	< 0.001	[redacted]	[redacted]	-	< 0.001	[redacted]	[redacted]	-

AE = adverse event; CI = confidence interval; DB = double-blind; FEV_1 = forced expiratory volume in one second; FDC = fixed-dose combination; FRC = functional residual capacity; IC = inspiratory capacity; L = litre; LS = least squares; MD = mean difference; N = number of patients; *P* = probability; RV = residual volume; SE = standard error; UMEC = umeclidinium; UMEC/VI = umeclidinium/vilanterol; VI = vilanterol; vs. = versus.
Note: ANCOVA model with covariates of treatment, baseline, smoking status, and centre group.
[a] Refer to Table 13 for baseline data on reported outcomes.
[b] For this review, mortality (death) is considered an efficacy outcome.
[c] Response was defined as a TDI focal score of at least 1 unit. Non-response was defined as a TDI focal score of less than 1 unit or a missing TDI focal score with no subsequent non-missing TDI assessments.
[d] Response was defined as a SGRQ total score of 4 units below baseline (score prior to dosing on day 1) or lower. Non-response was defined as a SGRQ total score higher than 4 units below baseline, or a missing change from baseline in SGRQ total score with no subsequent non-missing scores.
[e] In these studies, COPD exacerbations were considered under lack of efficacy, not AEs.
Source: Clinical Study Reports for DB2114417 and DB2114418.[8,10]

APPENDIX 5: 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 second (FEV_1)
- St. George's Respiratory Questionnaire (SGRQ)
- Transition Dyspnea Index (TDI)
- Modified Borg scale
- EuroQol 5-Dimensions Questionnaire (EQ-5D)
- Exercise endurance time (EET).

Findings

FEV_1, SGRQ, TDI, EQ-5D, and EET are briefly summarized in Table 29.

TABLE 29: 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	30,33
SGRQ	A disease-specific measure of HRQoL that consists of 50 items and was specifically developed for patients with chronic airflow limitation. The questionnaire is divided into 3 dimensions: Symptoms, Activity, and Impacts of the disease. The total score ranges from 0 to 100, where 0 indicates no impairment and 100 indicates worst.	Yes	4.0	21-23,34
TDI	Self-administered. TDI 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 severity of dyspnea.	Yes	1 unit	29
Modified Borg scale	11-point scale (ranges from 0 [no dyspnea] to 10 [max dyspnea] points).	Yes	1 unit	24-28
EQ-5D	A generic, self-reported measure of HRQoL that contains the EQ-5D descriptive system and the EQ VAS. The descriptive system contains 5 dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression; each dimension has	Yes	In general 0.033 to 0.74 COPD-specific 0.01 to 0.03	35-39

Instrument	Type	Evidence of Validity	MCID[a]	References
	3 levels (EQ-5D-3L; marks range from 1 to 3) or 5 levels (EQ-5D-5L; marks range from 1 to 5). A single summary index can be generated for the descriptive system. The EQ VAS has a score that ranges from 0 to 100.			
EET	EET was measured in an ESWT, which is a standardized constant-paced field test for the assessment of endurance capacity in patients with chronic lung disease.	unknown	70 secs 45 secs to 85 secs	40-43 44

EET = exercise endurance time; EQ = EuroQol; EQ VAS = EuroQol Visual Analogue Scale; EQ-5D = EuroQol 5-Dimensions Questionnaire; ESWT = enhanced shuttle walk test; FEV_1= forced expiratory volume in one second; HRQoL = health-related quality of life; L = litre; max = maximum; MCID = minimal clinically important difference; secs = seconds; SGRQ = St. George's Respiratory Questionnaire; TDI = Transition Dyspnea Index.
[a] MCID has not been determined between two active treatment groups.

Forced Expiratory Volume in One Second

FEV_1 is the volume of air that, after a full inspiration, can be forcibly expired in one second. This measure is commonly used both in clinical practice and in clinical trials and is generally thought to correlate with chronic obstructive pulmonary disease (COPD) outcomes.[3,45] In clinical practice, FEV_1 is used to grade risk of death in COPD patients.[46] 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.[30,33] Previous research indicated that relative change rather than absolute change may be more meaningful in patients with worse airflow limitation.[30] There is evidence that for patients who are undergoing COPD exacerbation, a two-day increase of 0.10 L reduced the relative risk of treatment failure by 20%.[45] However, changes of the same magnitude are not always associated with clinically important differences in all studies.

While both pre- and post-bronchodilator FEV_1 values have been reported to be indicators of health status, risk of death, and measure of severity in COPD, the Global Initiative for Chronic Lung Disease (GOLD) criteria indicate that post-bronchodilator values should be used.[46] 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.[46] 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 with pre-bronchodilator per cent predicted FEV_1 ($P = 0.009$ versus 0.131).

Normalized area under the curve (AUC) FEV_1 is an average of the measurement of bronchodilation over at least 80% of the duration of action after a single inhalation.[47] No information regarding the validity of this outcome or the MCID was identified.

St. George's Respiratory Questionnaire

The SGRQ is a disease-specific measure of HRQoL that consists of 50 items and was specifically developed for patients with chronic airflow limitation.[34] It was developed in 1992 to measure impaired health and perceived well-being in patients with airway disease, and to meet the need for a sensitive measure of HRQoL.[48] The instrument has been used worldwide in studies and in clinical settings.[48] The SGRQ questionnaire includes questions regarding sleep disturbances, public embarrassment, and panic (which can be signs of depression or anxiety), as well as feeling like a nuisance to friends and family, employment, and recreation activities (which are indicative of social impact).[49]

The 50 items of the questionnaire are divided into three dimensions: *Symptoms* (eight items measuring the distress due to respiratory symptoms), *Activity* (16 items measuring the effect of disturbances on mobility and physical activity), and *Impacts* (26 items measuring the psychosocial impact of the disease).[21] Items are weighted using empirically derived weights in order to determine the total SGRQ, which ranges from 0 to 100, where 0 indicates no impairment and 100 indicates worst possible health.[21,22] The generally accepted MCID for a change in total SGRQ from baseline is 4.0 units of change, and a decrease in scores indicates an improvement in HRQoL.[23] These have been examined as within-group measures, not between-group measures. As all estimates of clinical significance are subject to measurement error, sample error, and require value judgments, MCID should be interpreted as a general guidance[23] and it is unclear what between-group MCID would be clinically meaningful.

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 five-point scale where the low scores indicate no symptoms and high scores indicate more severe symptoms.[21] A number of items in the *Symptoms* component relate to the frequency of symptoms over the previous year.[50] Responses on the other two domains are mostly yes-no in nature. The *Activity* domain deals with mobility and physical activity problems that either cause or are limited by breathlessness.[21] 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).[50]

Transition Dyspnea Index

The Transition Dyspnea Index (TDI) is an interviewer-administered multidimensional instrument used to measure the severity of dyspnea.[29,51] It was developed by Mahler et al. in 1984. When used to determine breathlessness in patients at baseline, it is called 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 in TDI. At baseline, dyspnea is rated by items in BDI in five grades ranging from 0 (severe) to 4 (unimpairment). 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. Lower TDI score indicates more deterioration in 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.[52] A 1-unit change in TDI was considered to be the MCID.[29]

Modified Borg Dyspnea Index

The modified Borg dyspnea score is a categorical scale from 0 to 10, where 0 represents no dyspnea and 10 represents maximal dyspnea.[24] 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.[25-27] The MCID has been estimated to be 1 unit.[28]

EuroQol 5-Dimensions Questionnaire

EQ-5D was developed by the EuroQol Group, a network of international multidisciplinary researchers devoted to the measurement of health status.[35] It is a generic, self-reported health status assessment tool that measures the respondent's immediate situation. It may be applied to a wide range of health conditions and treatments. The EQ-5D 3-level version (EQ-5D-3L) was introduced in 1990 and consists of two parts: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system contains 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; each dimension has 3 levels: no problems (mark = 1), some problems (mark = 2) and extreme problems (mark = 3). Each state is referred to in terms of a 5-digit code, for instance, state 112233 indicates no problems with mobility and self-care, some problems with performing usual activities, moderate pain or discomfort and extreme anxiety or depression. EQ-5D health states that are defined by the descriptive system can be converted into a single summary index by using a formula, when each of the levels in each dimension is weighted. This index value can be used in the calculation of quality-adjusted life-years (QALYs), which is an important outcome in economic evaluations of health care interventions. The EQ VAS records the respondent's self-rated health on a vertical VAS where the end points are labelled, "best imaginable health state, mark = 100" and, "worst imaginable health state, mark = 0". The EQ VAS scores are patient-based and are not representative of the general population.[35]

In 2005, a task force of the EuroQol Group developed a new version of the EQ-5D to increase the reliability and sensitivity of this instrument while maintaining feasibility and potentially reducing the ceiling effects. Five levels of severity in each of the existing five EQ-5D dimensions were introduced: no problems, slight problems, moderate problems, severe problems, and extreme problems; this new version of EQ-5D was named EQ-5D-5L. The EQ-5D-5L has been validated in a diverse patient population in multiple countries, including patient groups with chronic respiratory disease. Redistribution of responses from the EQ-5D-3L to EQ-5D-5L was validated for all dimensions and all levels. The measurement properties of EQ-5D-5L were superior to the EQ-5D-3L in terms of feasibility, ceiling effects, discriminatory power, and convergent validity.[36,37]

Hence, the EQ-5D produces three types of data for each respondent:

- A profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
- A population preference-weighted health index score based on the descriptive system
- A self-reported assessment of health status based on the EQ VAS.

One way of presenting data of descriptive system is by reporting the frequency or the proportion of reported problems for each level of each dimension. When presenting the summarized EQ-5D index and

the EQ VAS data, the mean values and the relevant standard deviation (or the 25th and 75th percentiles if the data are skewed) can be reported.[35]

The reported MCID for the EQ-5D estimated in COPD patients ranged between 0.011 to 0.03.[38,39] However, a generic health status instrument may not be adequately responsive to COPD-specific interventions.[30]

Exercise Endurance Time

The European Medicines Agency (EMA) recommends that enhanced exercise capacity be a co-primary end point with lung function improvements.[43] In the included studies of the current review, endurance walking capacity or exercise endurance time (EET) was measured in the endurance shuttle walk test (ESWT). 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.[40,41]

Before each ESWT, 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 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 m 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 warm-up, each patient's walking speed was set at the speed corresponding to 80% of peak oxygen consumption, as predicted from an incremental shuttle walking test (ISWT) at baseline. [40] During the ESWT, 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 in which the patient carried out the walk. EET was expressed in seconds.

There are no widely accepted MCIDs for EET and ESWT. Previous research suggested a difference of 70 seconds (95% CI, 46 seconds to 95 seconds) as a clinically important difference for within-patient comparisons of EET.[42] A difference of 45 seconds to 85 seconds was suggested as MCID for EET in more recent clinical studies.[44]

Summary

FEV_1, SGRQ, TDI, and EQ-5D have all been shown to be valid outcome measures for patients with COPD, although EQ-5D as a generic health status instrument may not be adequately responsive to COPD-specific interventions. The suggested MCIDs for FEV_1, SGRQ, TDI, and EQ-5D were 0.1 to 0.14 L, four units change from baseline, 1 unit change from baseline, and 0.01 to 0.03 units change from baseline, respectively.

EET was recommended by EMA as a co-primary end point with lung function improvements. No information on the validation of this outcome measure was reported. A difference of 70 seconds, or a range between 45 seconds and 85 seconds based on more recent evidence, was considered acceptable as an MCID for within-patient comparisons of EET.

APPENDIX 6: SUMMARY OF DRY POWDER INHALERS

Aim

To describe the characteristics regarding ease of use and correct use, as well as patient satisfaction with the Anoro Ellipta inhaler device and the Spiriva HandiHaler used in patients with chronic obstructive pulmonary disease (COPD).

Findings

The characteristics of the dry powder inhaler are summarized below.

Characteristics of the Inhalers

Anoro Ellipta is delivered with the Ellipta inhaler device, a multi-dose dry powder inhaler. Each inhaler contains two double-foil blister strips of powder formulation with one month's supply (one dose per day for 30 days). Each dose contains umeclidinium 62.5 mcg in one blister and vilanterol 25 mcg in another blister.[53] After the inhaler is activated, the powder within both blisters is exposed and ready for dispersion into the airstream created by the patient inhaling through the mouthpiece. Each time the patient fully opens the cover of the inhaler (which can be confirmed by hearing a clicking sound), a dose is ready to be inhaled. This is also shown by a decrease in the number on the counter. If the patient opens and closes the cover without inhaling the medicine, that dose will be lost. The lost dose will be held in the inhaler, but it will no longer be available to be inhaled; therefore the patient will not accidentally take a double dose or an extra dose in one inhalation. There is no indicator that tells a patient that the dose has been properly delivered or inhaled.[53]

Tiotropium bromide is delivered through the HandiHaler device.[54] The patient must open the dust cap, open the mouthpiece, remove a capsule from a blister package, place the capsule in the inhaler, push and release a button to crush the capsule, fully exhale, then inhale the dry powder. In order to ensure the full dose is achieved, the patient must then fully exhale and inhale any remaining dry powder. There is no indicator that tells a patient that the dose has been properly loaded and is ready to inhale, but the patient should be able to hear the capsule vibrating as an indicator that the dose has been properly inhaled.

More details regarding the characteristics of each inhaler are included in Table 26.

TABLE 30: INHALER CHARACTERISTICS

Characteristic	Ellipta[53]	Spiriva HandiHaler[54,55]
Preloaded/Multi-dose	Yes — multiple doses come loaded in inhaler; patient opens the cover of the inhaler fully to load a dose.	No — patient must remove tablet from blister package and insert into inhaler.[a]
Confirmation that dose is ready	Auditory — a clicking sound indicates a dose is ready to be inhaled. This is also shown by a decrease in the number on the counter.	No — auditory click that the mouthpiece has been properly secured, but nothing to indicate dose is ready.
Confirmation of dose delivery	No audible or visible sign. Dose delivery is based on inhaling correctly. Patient may not taste or feel the medicine. If patient opens and closes the cover without inhaling the medicine, patient will lose the dose.	Yes — patient can hear and feel capsule vibrate in the device chamber; may taste sweet.
Number of inhalations required	1, once daily	2, once daily
Requires step after inhalation	No	Yes — must remove used capsule from the chamber after use.
Inhaler requires cleaning	Routine cleaning is not required. Can clean the mouthpiece if needed, using a dry tissue, before closing the cover.	Once per month.

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

Patient Use of Inhalers

It was reported that in clinical trials, 98% of patients used Ellipta correctly following a single instruction.[56,57] Based on recall, 55% to 68% of COPD patients preferred Ellipta versus 7% to 21% who preferred the HandiHaler device. In an exploratory exit survey of patient preference from phase 3 studies, 95% of the surveyed patients (19 out of 20) preferred the Ellipta device over HandiHaler.[58] A direct link between the use of the Ellipta device and improved adherence has not been established, but it was suggested that a preference for a particular inhaler device may be associated with improved adherence to a therapeutic regimen.[59]

Limitations

The primary limitation of the patient satisfaction and ease of use studies is that they were sponsored by manufacturers. There were no data on the level of instruction or training reported. No information was provided regarding comorbid conditions that may affect the use of the devices, such as arthritis or cognitive difficulties.

Summary

The Ellipta device is a multi-dose, preloaded inhaler, whereas the HandiHaler requires the patient to load each dose capsule into the inhaler prior to use. The Ellipta inhaler requires only one inhalation of the dry powder once a day, but the HandiHaler requires two inhalations once a day. Overall, the manufacturer-sponsored studies suggested that the Ellipta inhaler device seems to be favoured by patients with COPD compared with other inhalers such as the Spiriva HandiHaler.

APPENDIX 7: CRITICAL APPRAISAL OF MANUFACTURER-SUBMITTED INDIRECT TREATMENT COMPARISON BETWEEN ANORO ELLIPTA AND OTHER DRUG THERAPIES

1. Objectives

The manufacturer submitted an indirect treatment comparison (ITC) between umeclidinium/vilanterol (UMEC/VI) and other bronchodilators including long-acting beta2-agonist (LABA)/long-acting muscarinic antagonist (LAMA) combinations, ICS plus LABA plus LAMA combinations, and indacaterol/glycopyrronium (IND/GLY) in the treatment of chronic obstructive pulmonary disease (COPD). The objective of this review is to provide a summary and critical appraisal of the manufacturer-provided ITC.

2. Summary of Indirect Comparison Analysis

Rationale

Long-acting bronchodilators for COPD were recommended in the current practice guidelines. In addition, combined bronchodilators of different pharmacology classes were considered as a better alternative for COPD management. Since no head-to-head randomized trials comparing UMEC/VI with other combined bronchodilation therapies were identified through a systematic literature search, an ITC was performed by the manufacturer to estimate the comparative efficacy of UMEC/VI to the appropriate comparators.

Methods

Eligibility Criteria

The inclusion criteria for the ITC consisted of the following:

- COPD patients ≥ 35 years of age and eligible for COPD maintenance therapy
- Randomized controlled trials (RCTs) reporting results for indacaterol/tiotropium combination (IND/TIO), fluticasone/salmeterol plus tiotropium combination (FLUT/SAL plus TIO) and indacaterol/glycopyrronium combination (IND/GLY)
- Phase 3 or 4 RCTs with parallel groups and a study duration of at least 12 weeks
- Measured outcome of lung function, health-related quality of life (HRQoL), COPD symptoms, or rescue medication use.

In order to identify relevant studies for this ITC, a systematic review was performed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Details regarding the literature search strategy, study selection, and data extraction of this systematic review were reported in separate documents.[60,61] In this systematic review, the literature was searched in multiple databases on October 15, 2013 and later updated in April 2014, using predefined search strategies. The risk of bias at the study level was assessed on the basis of the adequacy of the randomization, allocation concealment, blinding of patient and therapist, and complete and non-selective results reporting. The risk of bias at the outcome level was assessed on the basis of the adequacy of blinding of the end point collectors, implementation of the intention-to-treat (ITT) principle, and complete and non-selective results reporting.

Interventions and Comparators

The interventions included in the indirect comparison analysis were UMEC/VI (62.5 mcg/25 mcg once daily), IND/TIO (150 mcg/18 mcg once daily), FLUT/SAL plus TIO (500 mcg/50 mcg plus 18 mcg once daily) and IND/GLY (110 mcg/50 mcg once daily).

Outcomes

Studies reporting one of the following outcomes were included: change in trough forced expiratory volume in one second (FEV_1), St. George's Respiratory Questionnaire (SGRQ) total score, Transition Dyspnea Index (TDI) focal score, or rescue medication use at week 12 and week 24. The outcomes of interest were determined by the manufacturer prior to the analysis, based on payer requirements and results of the manufacturer's systematic review.

Analysis

The Bucher approach was employed in the ITC. The first step was to generate a pooled mean difference in change from baseline for each treatment of interest relative to a common comparator using traditional pairwise random-effect meta-analyses. The second step was to indirectly estimate the relative effectiveness of the investigating drug (UMEC/VI) to the comparators.

In the first step, point estimates and 95% confidence intervals (CIs) for continuous variables were reported, while the number of events and relative risk (RR) were reported for dichotomous variables. Results for the ITC were presented as RR with 95% CI and corresponding probability (*P*) value.

The statistical heterogeneity was assessed by means of the Cochran Q, chi-square test and the I^2 statistic with 95% CI, while the clinical heterogeneity was assessed by means of: 1) study design; 2) inclusion criteria related to FEV_1, FEV_1/forced vital capacity (FVC), exacerbations and smoking status; 3) background treatment with inhaled corticosteroids (ICS) and/or LABA; 4) randomization; 5) blinding; 6) open-label groups; and 7) crossover design. Patient baseline characteristics were also considered: exacerbation history, proportion of patients per COPD severity level, COPD duration, mean per cent predicted FEV_1, proportion of current smokers, mean pack-years, percentage of male patients, and mean age. When confounders and/or effect modifiers were suspected, a separate analysis was conducted to explore the degree to which base case findings were affected by excluding the evidence where such clinical heterogeneity existed. Random-effect meta-regression was not performed due to the low number of included studies.[60]

The authors indicated that there were no clear guidelines available on the power calculations for ITC and network meta-analysis (NMA). Post-hoc estimation of the power was conducted instead by using the frequentist approach.[62]

There were no details regarding the determination of publication bias, although the authors indicated that one limitation of their systematic review was publication bias.[61]

Results

Study and Patient Characteristics

A total of 11 RCTs were identified in the systematic review; therefore, they were included in this ITC. Four of these were UMEC/VI trials (DB2113360, DB2113374, DB2113373, and ZEP117115), two for IND/TIO (INTRUST 1 and INTRUST 2), two for FLUT/SAL plus TIO (Cazzola 2007 and Aaron 2007), and three for IND/GLY (ENLIGHTEN, SPARK, and SHINE). The four UMEC/VI studies were also included in the current CADTH Common Drug Review (CDR). Tiotropium 18 mcg or placebo was the common

comparator in the ITC with the investigating drugs. These 11 trials were all randomized, DB, multi-centre parallel trials. The study duration ranged from 12 weeks to 64 weeks.

The inclusion criteria in these trials varied in terms of post-bronchodilator FEV_1: eligible participants were required to have post-bronchodilator $FEV_1 \leq 50\%$ in two trials, $\leq 65\%$ in three trials, and $\leq 70\%$ in four trials. $FEV_1/FVC < 0.70$ was required in all trials. Stable dose of ICS was allowed as background treatment in nine trials, but not permitted in two FLUT/SAL plus TIO trials (conducted in 2007); salbutamol or albuterol were allowed as rescue medication in all trials.

The number of enrolled patients in these 11 trials ranged from 60 to 1,483. Significant heterogeneity existed in the baseline patient characteristics across all trials: mean age ranged from 61.9 years to 68.1 years, majority of the patients were male (proportion of males ranged from 53.8% to 93%), proportion of current smokers ranged from 26.9% to 83.3%, proportion of patients with severe or very severe COPD varied from 19.5% to 100%, ICS use varied from 0% to 76%, and the time since COPD diagnosis ranged from 5.5 years to 11.3 years. Baseline per cent predicted FEV_1 ranged from 37.0 to 59.4. Among the four UMEC/VI trials, the patient's baseline characteristics were comparable. Percentage of reversibility post-salbutamol and proportion of patients with exacerbations in the year prior to randomization were not reported in this report.

One of the IND/GLY studies, the SPARK trial (TIO compared with IND/GLY in 64 weeks), differed from other studies in that all enrolled patients had severe or very severe COPD, had history of at least one exacerbation in the previous 12 months, and had the lowest FEV_1 compared with the other 10 trials. This was the largest trial among the 11. Sensitivity analyses were performed in data analysis to evaluate the impact of inclusion or exclusion of SPARK on the results of the ITC.

Results of the Indirect Treatment Comparison

Change From Baseline for Trough FEV_1

Week 12: When conducting ITC between UMEC/VI and IND/TIO, results on this outcome from three UMEC/VI trials (DB2113360, DB2113374, and ZEP117115) and two IND/TIO trials (INTRUST1 and INTRUST2) were pooled separately in two meta-analyses. The trials synthesized by each meta-analysis were highly homogeneous, due to the comparable patient characteristics at baseline and the study design. There was no statistically significant difference between UMEC/VI and IND/TIO for this outcome, and the between-group difference was lower than the MCID of trough FEV_1 (100 mL).

When conducting ITC between UMEC/VI and FLUT/SAL plus TIO, results on this outcome from four studies were used (three UMEC/VI trials: DB2113360, DB2113374, and ZEP117115; one FLUT/SAL plus TIO trial: Cazzola 2007), and data from the three UMEC/VI trials were pooled. Tests for heterogeneity were not statistically significant. The difference between UMEC/TIO and FLUT/SAL plus TIO was statistically significant for this outcome (difference: 54 mL, 95% CI, 12.80 to 95.19; $P = 0.01$); however, the between-group difference was lower than the MCID of trough FEV_1 (100 mL).

When conducting ITC between UMEC/VI and IND/GLY, results on this outcome from seven studies (four UMEC/VI trials: DB2113360, DB2113374, DB2113373, and ZEP117115; three IND/GLY trials: ENLIGHTEN, SPARK, and SHINE) were pooled separately in two different meta-analyses. The trials synthesized by each meta-analysis were highly homogeneous. ITC results indicated that there was no statistically significant difference between UMEC/VI and IND/GLY for this outcome (difference: 10.45 mL, 95% CI, 22.51 to 43.41; $P = 0.535$), and the between-group difference was lower than the MCID of trough FEV_1

(100 mL). When excluding the SPARK trial, there was no major impact on the results of the ITC (between-group difference: –2.22 mL, 95% CI, –35.96 to 31.51; *P* = 0.897).

Week 20 to Week 24

In the ITC between UMEC/VI and FLUT/SAL plus TIO, four trials (three UMEC/VI trials: DB2113360, DB2113374, and ZEP117115; one FLUT/SAL plus TIO trial: Aaron 2007) reported data on this outcome at week 20 or week 24. There was no statistically significant heterogeneity across the UMEC/VI trials. The pooled estimates of the trough FEV_1 at week 20/24 in the three UMEC/VI trials were comparable with that in the FLUT/SAL plus TIO trial, and the between-group difference was not statistically or clinically significant (difference: 21.17 mL, 95% CI, –46.20 to 88.55; *P* = 0.54).

When conducting ITC between UMEC/VI and IND/GLY, results on this outcome from seven studies (four UMEC/VI trials: DB2113360, DB2113374, DB2113373, and ZEP117115; three IND/GLY trials: ENLIGHTEN, SPARK, and SHINE) were pooled in two separate meta-analyses. Tests for heterogeneity were not statistically significant for the UMEC/VI trials or the IND/GLY trials. There was no statistically significant difference between UMEC/VI and IND/GLY for this outcome (difference: 6.99 mL, 95% CI, –24.05 to 38.02; *P* = 0.659). When excluding the SPARK trial, there was no major impact on the results of the ITC (between-group difference: –2.52 mL, 95% CI, –30.25 to 35.28; *P* = 0.880).

Details are presented in Table 31.

TABLE 31: TROUGH FORCED EXPIRATORY VOLUME IN ONE SECOND AT WEEK 12 AND WEEK 24 (ML), INDIRECT TREATMENT COMPARISON RESULTS

	Comparator Treatment	Reference Treatment	
		TIO	Placebo
Trough FEV_1 at week 12 (mean difference from baseline, 95% CI)	UMEC/VI	–99.00 (–121.27 to –76.72), favouring UMEC/VI	NA
	IND/TIO	–73.90 (–89.52 to –58.29), favouring IND/TIO	NA
	ITC between UMEC/VI and IND/TIO: 25.10 (–2.11 to 52.30), *P* = 0.071		
	UMEC/VI	–99 (–121.27 to –76.72), favouring UMEC/VI	NA
	FLUT/SAL+TIO (1 study)	–45 (–79.66 to –10.34), favouring FLUT/SAL+TIO	NA
	ITC between UMEC/VI and FLUT/SAL+TIO: 54.00 (12.80 to 95.19), *P* = 0.01		
	UMEC/VI	–99.00 (–121.27 to –76.72), favouring UMEC/VI	–195 (–230 to –160), favouring UMEC/VI
	IND/GLY	–84.23 (–113.59 to –54.87), favouring IND/GLY	–201.83 (–266.65 to –137.01), favouring IND/GLY
	ITC between UMEC/VI and IND/GLY: 10.45 (–22.51 to 43.41), *P* = 0.535		
Trough FEV_1 at week 20/24 (mean difference from baseline, 95% CI)	UMEC/VI	–92.17 (–122.82 to –61.52), favouring UMEC/VI	NA
	FLUT/SAL+TIO (1 study)	–71 (–130 to –10), favouring FLUT/SAL+TIO	NA

	Comparator Treatment	Reference Treatment	
		TIO	Placebo
	ITC between UMEC/VI and FLUT/SAL+TIO: 21.17 (–46.20 to 88.55), *P* = 0.538		
	UMEC/VI	–92.17 (–122.82 to –61.52), favouring UMEC/VI	–167 (–207 to –128), favouring UMEC/VI
	IND/GLY	–75.38 (–93.73 to –57.04), favouring IND/GLY	–185.59 (–228.71 to –142.47), favouring IND/GLY
	ITC between UMEC/VI and IND/GLY: 6.99 (-24.05, 38.02), p = 0.659		

CI = confidence interval; FEV_1= forced expiratory volume in one second; FLUT/SAL+TIO = fluticasone/salmeterol plus tiotropium; IND/GLY = indacaterol/glycopyrronium; IND/TIO = indacaterol/tiotropium; ITC = indirect treatment comparison; NA = not applicable; *P* = probability; TIO = tiotropium; UMEC/VI = umeclidinium/vilanterol.
Data source: Manufacturer-submitted ITC.

Rescue Medication Use (Decrease in Number of Puffs/Day)

Week 12: Four trials (two UMEC/VI trials: DB2113360 and DB2113374; two IND/TIO trials: INTRUST1 and INTRUST2) reported data on this outcome at week 12; therefore, they were included in the ITC of UMEC/VI versus IND/TIO. There was no statistically significant heterogeneity across the UMEC/VI trials, or the IND/TIO trials. The pooled estimates of the decrease in the number of rescue medication uses per day were comparable between the two drugs, and the between-group difference was not statistically significant (difference: 0.24 puffs/day, 95% CI, –0.34 to 0.82; *P* = 0.426) (Table 32).

Week 24: Four UMEC/VI trials (DB2113373, DB2113360, DB2113374, and ZEP117115) and one IND/GLY trial (SHINE) reported data on this outcome. There was no statistically significant heterogeneity across the UMEC/VI trials. The pooled estimates of the decrease in the number of rescue medication uses per day at week 24 were comparable with that in the IND/GLY trial, and the between-group difference was not statistically significant (difference: 0.04 puffs/day, 95% CI, –0.24 to 0.33; *P* = 0.765).

Details are presented in Table 32.

TABLE 32: DECREASE IN RESCUE MEDICATION USE PER DAY AT WEEK 12, INDIRECT TREATMENT COMPARISON RESULTS

	Comparator Treatment	Reference Treatment	
		TIO	Placebo
Rescue medication use at week 12 (mean difference from baseline in decrease in number of puffs/day, 95% CI)	UMEC/VI	0.65 (0.22 to 1.08), favouring UMEC/VI	NA
	IND/TIO	0.89 (0.50 to 1.28), favouring IND/TIO	NA
	ITC between UMEC/VI and IND/TIO: 0.24, (–0.34 to 0.82), *P* = 0.426		
Rescue medication use at week 24 (mean difference from baseline in decrease in number of puffs/day, 95% CI)	UMEC/VI	0.54 (0.33 to 0.76), favouring UMEC/VI	NA
	IND/GLY	0.89 (0.50 to 1.28), favouring IND/TIO	NA
	ITC between UMEC/VI and IND/TIO: 0.04 (–0.24 to 0.33), *P* = 0.765		

CI = confidence interval; IND/GLY = indacaterol/glycopyrronium; IND/TIO = indacaterol/tiotropium; ITC = indirect treatment comparison; NA = not applicable; *P* = probability; TIO = tiotropium; UMEC/VI = umeclidinium/vilanterol.
Data source: Manufacturer-submitted ITC.

Change from Baseline for SGRQ Total Score

Week 12: Four trials (three UMEC/VI trials: DB2113360, DB2113374, and ZEP117115; one IND/GLY trial: SPARK) reported SGRQ total score at week 12. Data from the UMEC/VI trials were pooled and the results favoured UMEC/VI when compared with TIO. In the IND/GLY trial, the results favoured IND/GLY when compared with TIO. Results of ITC indicated that there was no statistically significant difference between UMEC/VI and IND/GLY for this outcome (difference: 1.27, 95% CI, –0.77 to 3.31; *P* = 0.222). Lower SGRQ score indicates improved quality of life.

Week 24: Six studies were identified in the systematic review that reported this outcome at week 24: four UMEC/VI trials (compared with TIO in DB2113360, DB2113374, and ZEP117115; compared with placebo in DB2113373) and two IND/GLY trials (compared with TIO in SPARK; compared with TIO and placebo in SHINE). There was no statistically significant difference between UMEC/VI and IND/GLY for this outcome (difference: –0.50 units, 95% CI, –4.01 to 3.02; *P* = 0.782). Excluding SPARK from the analysis did not have a major influence on the ITC results (between-group difference: –0.44 units, 95% CI, –4.13 to 3.25;
P = 0.817).

Details are presented in Table 33.

TABLE 33: CHANGE FROM BASELINE FOR ST. GEORGE'S RESPIRATORY QUESTIONNAIRE TOTAL SCORE AT WEEK 12 AND WEEK 24, INDIRECT TREATMENT COMPARISON RESULTS

	Comparator Treatment	Reference Treatment	
		TIO	Placebo
Between-group difference in SGRQ score at week 12 (mean difference from baseline, 95% CI)	UMEC/VI	1.73 (0.65 to 2.81), favouring UMEC/VI	NA
	IND/GLY (1 study)	3.0 (1.27 to 4.73), favouring IND/GLY	NA
	ITC between UMEC/VI and IND/GLY: 1.27 (–0.77 to 3.31), *P* = 0.222		
Between-group difference in SGRQ score at week 24 (mean difference from baseline, 95% CI)	UMEC/VI	0.85 (–0.94 to 2.65), favouring UMEC/VI	5.51 (3.13 to 7.88), favouring UMEC/VI
	IND/GLY	1.96 (0.94 to 2.98), favouring IND/GLY	3.01 (0.97 to 5.05), favouring IND/GLY
	ITC between UMEC/VI and IND/GLY: –0.50 (–4.01 to 3.02), *P* = 0.782		

CI = confidence interval; IND/GLY = indacaterol/glycopyrronium; ITC = indirect treatment comparison; NA = not applicable; *P* = probability; SGRQ = St. George's Respiratory Questionnaire; TIO = tiotropium; UMEC/VI = umeclidinium/vilanterol.
Data source: Manufacturer-submitted ITC.

TDI Focal Score

Week 12: Four studies were identified in the systematic review that reported this outcome at week 12: three UMEC/VI trials (compared to TIO in DB2113360 and DB2113374; compared to placebo in DB2113373) and one IND/GLY trial (compared to TIO and placebo in SHINE). There was no statistically significant difference between UMEC/VI and IND/GLY for this outcome (difference: –0.07 units, 95% CI, –0.54 to 0.40; *P* = 0.764).

Week 24: At week 24, three UMEC/VI trials (compared to TIO in DB2113360 and DB2113374; compared to placebo in DB2113373) and one IND/GLY trial (compared to TIO and placebo in SHINE) were included in ITC. There was no statistically significant between-group difference for UMEC/VI versus IND/GLY (difference: –0.23 units, 95% CI, –0.80 to 0.34; *P* = 0.423).

Details are presented in Table 34.

TABLE 34: CHANGE FROM BASELINE FOR TRANSITION DYSPNEA INDEX FOCAL SCORE AT WEEK 12 AND WEEK 24, INDIRECT TREATMENT COMPARISON RESULTS

	Comparator Treatment	Reference Treatment	
		TIO	Placebo
Between-group difference in TDI focal score at week 12 (mean difference from baseline, 95% CI)	UMEC/VI	–0.42 (–0.91 to 0.07), favouring UMEC/VI	–1.3 (–1.7 to –0.8), favouring UMEC/VI
	IND/GLY	–0.63 (–1.06 to –0.20), favouring IND/GLY	–1.22 (–1.73 to –0.71), favouring IND/GLY
	ITC between UMEC/VI and IND/GLY: –0.07 (–0.54 to 0.40), *P* = 0.764		
Between-group difference in TDI focal score at week 24 (mean difference from baseline, 95% CI)	UMEC/VI	–0.03 (–0.48 to 0.43), favouring UMEC/VI	–1.2 (–1.7 to –0.7), favouring UMEC/VI
	IND/GLY	–0.51 (–0.74 to –0.28), favouring IND/GLY	–1.09 (–1.57, to –0.61), favouring IND/GLY
	ITC between UMEC/VI and IND/GLY: –0.23 (–0.80 to 0.34), *P* = 0.423		

CI = confidence interval; IND/GLY = indacaterol/glycopyrronium; ITC = indirect treatment comparison; *P* = probability; TDI = Transition Dyspnea Index; TIO = tiotropium; UMEC/VI = umeclidinium/vilanterol.
Data source: Manufacturer-submitted ITC.

3. Critical Appraisal of Indirect Treatment Comparison

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.[63] Details and commentary for each of the relevant items identified by the ISPOR group are provided in Table 35.

Limitations

Only a high-level summary of methods and results of the ITC was provided in the manufacturer submission. Details related to the literature search strategy, study selection, data extraction, and quality assessment of the included studies were reported in a different document without sufficient details. The lack of details led to the following concerns:

- Insufficient details were provided with respect to the key patient characteristics (e.g., exacerbation in the year prior to randomization, type and severity of COPD, previous COPD management, and reversibility to salbutamol) and trial characteristics (such as patient withdrawal). Thus, it was impossible to comprehensively address heterogeneity on important factors across the included studies. This is important because the validity of indirect comparisons rests on a sufficient degree of comparability in methods, populations, and outcome definitions across studies.
- No data were reported on patient withdrawal. Approaches used in quality assessment of the included studies were briefly described; however, no results were reported. It is therefore difficult to evaluate the internal validity of individual trials included in the ITC.

In terms of clinical heterogeneity, the treatment duration and patient baseline characteristics varied substantially across the included studies of combined long-acting bronchodilators. In addition, the authors stated that publication bias was one of the limitations of the systematic review.

A number of key outcomes identified in the CDR systematic review were not evaluated in the ITC. These included exacerbations, exercise tolerance, and safety outcomes. The outcomes of interest in this report were identified by the manufacturer based on payer requirements and results of the manufacturer's systematic review. These gaps limit the ability to assess the comparative benefits and harms of UMEC/VI specifically versus other combined long-acting bronchodilators. In addition, there is a lack of well-established approaches for power calculation in ITC; therefore, post-hoc estimation was adopted in the current study. The differences observed between UMEC/VI and other combined bronchodilators in all the outcome measures did not appear to be clinically relevant according to the MCIDs; therefore, power is not a big concern in this ITC.

Strengths

A systematic literature search was performed, according to the authors. Power calculation was conducted even though a well-established approach specific for ITC was not yet available. Subgroup analysis was conducted to explore the degree of impact of a study with high heterogeneity on the ITC results.

TABLE 35: APPRAISAL OF THE INDIRECT COMPARISON ANALYSES USING INTERNATIONAL SOCIETY FOR PHARMACOECONOMICS AND OUTCOMES RESEARCH CRITERIA

ISPOR Checklist Item		Details and Comments
1.	Are the rationale for the study and the objectives stated clearly?	• The rationale for conducting an indirect comparison analysis and the study objectives were clearly stated.
2.	Does the Methods section include the following: • Eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction • Validity of individual studies?	• The eligibility criteria for individual RCTs were presented. • Details regarding literature search, study selection, and data extraction were provided. • Methods of quality assessment of included studies were described; however, the results were not provided.
3.	Are the outcome measures described?	• Outcomes assessed in the indirect comparison analysis (symptom scores and medication scores) were briefly described. • The outcomes of interest were determined by the manufacturer. • No detailed information on the specific quality of life scales and symptom scores used in the analysis.
4.	Is there a description of methods for analysis or synthesis of evidence? • Description of analyses methods or models • Handling of potential bias/inconsistency • Analysis framework	• Indirect treatment comparison using the Bucher approach was on the outcomes of interest. Random-effect models were used in data synthesis. • Statistical and clinical heterogeneity were examined. • Publication bias was examined according to the authors, yet the method used to detect such a bias was not provided.

ISPOR Checklist Item		Details and Comments
5.	Are sensitivity analyses presented?	• Impact of a particular study on the study results was examined by including/excluding this study.
6.	Do the results include a summary of the studies included in the network of evidence? • Individual study data? • Network of studies?	• A table with trial characteristics of all included studies was provided. Also, there was a table of patient baseline characteristics in the included trials. There was no data presented on the definition of the quality of life instruments and symptom scales. • A figure showing the network of studies was provided. Forest plots of meta-analysis results between each of the three active comparators and the reference treatment were presented. • Tables with raw data by study and treatment were provided for the indirect comparison analysis.
7.	Does the study describe an assessment of model fit? Are competing models being compared?	• NA
8.	Are the results of the evidence synthesis presented clearly?	• The results of the analysis were clearly reported for each outcome measure, including point estimates and 95% confidence intervals as a measure of uncertainty.
9.	Sensitivity or scenario analyses	• Scenario analysis was reported.

ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NA = not applicable; RCTs = randomized controlled trials.

4. Summary

The manufacturer undertook a systematic review of RCTs and performed an indirect treatment analysis using the Bucher method to compare UMEC/VI with other combined long-acting bronchodilators. The results suggested that UMEC/VI is not statistically different from IND/TIO, FLUT/SAL plus TIO or IND/GLY in improving lung function (measured by change in FEV_1), the need for rescue medication use, improving HRQoL, and dyspnea symptoms for patients with COPD; the observed between-group differences were not clinically relevant according to the respective MCIDs. Given that no head-to-head trials of combined long-acting bronchodilator therapy were identified, and methodology of the current report remains unclear, the results of the ITC should be interpreted with caution. Further research such as meta-regression that includes covariates that may influence the clinical outcomes was suggested by the authors, as this may help to further explain any heterogeneity and identify differences among the various study drugs. As other efficacy and safety outcomes were not evaluated in this ITC, we are not able to estimate the other clinical benefits and risks for UMEC/VI relative to other comparators.

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