Common Drug Review
Clinical Review Report

January 2018

Drug	umeclidinium bromide (Incruse Ellipta)
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 other long-acting muscarinic antagonists (LAMAs) as a maintenance bronchodilator treatment for COPD.
Dosage form(s)	Dry powder for oral inhalation, 62.5 mcg per inhalation
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.

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

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ABBREVIATIONS

AE	adverse event
BDI	Baseline Dyspnea Index
CDR	CADTH Common Drug Review
COPD	chronic obstructive pulmonary disease
EDS	Exercise Dyspnea Scale
EET	exercise endurance time
EMA	European Medicines Agency
ESWT	endurance shuttle walk test
FEV_1	forced expiratory volume in one second
FRC	forced residual capacity
FVC	forced vital capacity
GOLD	Global Initiative for Obstructive Lung Disease
HRQoL	health-related quality of life
IC	inspiratory capacity
ICS	inhaled corticosteroid
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITC	indirect treatment comparison
ITT	intention-to-treat
LABA	long-acting beta2-agonist
LAMA	long-acting muscarinic antagonist
LS	least squares
MCID	minimal clinically important difference
RCT	randomized controlled trial
RV	residual volume
SAE	serious adverse event
SGRQ	St. George's Respiratory Questionnaire
TDI	Transition Dyspnea Index
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Chronic obstructive pulmonary disease (COPD) is a respiratory disorder characterized by progressive, partially reversible airway obstruction and lung hyperinflation, systemic manifestations, and increasing frequency and severity of exacerbations. COPD is a leading cause of morbidity and mortality worldwide, and is associated with high rates of hospital admissions and readmissions. Patients' everyday lives are affected, including their ability to breath, talk, sleep, work, and socialize. Patient groups report looking for drugs that can improve lung function and quality of life, reduce exacerbations, delay disease progression, and over the long term improve survival, rather than just providing symptomatic or emergency relief.

Pharmacotherapy in the form of long-acting bronchodilators is the mainstay of treatment for COPD. Umeclidinium bromide is a long-acting muscarinic antagonist (LAMA) that is approved for use in Canada as a long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including those with chronic bronchitis and emphysema. The recommended dose is 62.5 mcg once daily, administered as a dry powder, oral inhalation using the Ellipta device.

Indication under review
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 criteria requested by sponsor
List in a similar manner to other LAMAs as a maintenance bronchodilator treatment for COPD.

The objective of this systematic review was to evaluate the beneficial and harmful effects of umeclidinium bromide (Incruse) 62.5 mcg once daily delivered via the Ellipta dry powder inhaler (i.e., Incruse Ellipta) for the treatment of patients with COPD, including chronic bronchitis and emphysema.

Results and interpretation

Included studies

Six manufacturer-sponsored trials were included in the review. Two (DB2116132 and DB2116133) of the six studies were short-term (14-day), three-way, randomized crossover trials; however, due to a number of methodological limitations — i.e., primary outcome selection, statistical testing hierarchy, and the prioritization of treatment comparisons — the presentation of data from these studies is limited to Section 3.1 and Section 3.2.1 of this report.

The four remaining studies included two parallel-group, randomized controlled trials (RCTs) comparing umeclidinium 62.5 mcg to placebo over a 12-week (AC4115408) and 24-week (DB2113373) period, and two randomized crossover trials (DB2114417 and DB2114418) consisting of two 12-week treatment periods separated by a 14-day washout period designed to assess exercise endurance following treatment with umeclidinium/vilanterol versus placebo.

Trough forced expiratory volume in one second (FEV_1) was the primary outcome in the 12-week and 24-week parallel-group studies, and a co-primary end point alongside exercise endurance time (EET) in the exercise endurance studies. Secondary and other outcomes in the 12-week and 24-week parallel-group studies included Transition Dyspnea Index (TDI), St. George's Respiratory Questionnaire (SGRQ), rescue salbutamol use, and health care resource utilization (DB2113373 only), and in the exercise endurance studies included lung volumes (inspiratory capacity [IC], forced residual capacity [FRC], and residual volume [RV]), Exercise Dyspnea Scale (EDS), and rescue salbutamol use. The exercise endurance studies were not primarily designed to assess umeclidinium monotherapy versus placebo; umeclidinium 62.5 mcg versus placebo was considered an exploratory comparison.

All studies enrolled patients with moderate to severe COPD. The number of patients randomized to the umeclidinium 62.5 mcg groups varied across studies: 41 (DB2114418), 49 (DB2114417), 69 (AC4115408) and 418 (DB2113373). The number of patients randomized to the placebo groups also varied across studies: 68 (AC4115408), 151 (DB2114418), 170 (DB2114417), and 280 (DB2113373). The results for the comparisons between umeclidinium 62.5 mcg versus placebo are presented in this review; the results for the comparisons between umeclidinium/vilanterol 62.5 mcg/25 mcg and placebo can be found in the Anoro Ellipta CADTH Common Drug Review (CDR) clinical review report.[1] The results for comparisons between treatment groups that are not approved by Health Canada (umeclidinium 125 mcg, umeclidinium/vilanterol 125 mcg/25 mcg, and vilanterol 25 mcg) were excluded from this review.

The key limitations of the trials included in the review were the short study durations (12 weeks and 24 weeks); the study design; power calculations for the exercise endurance studies not being optimized for the comparison of interest in this review (umeclidinium 62.5 mcg versus placebo); and no direct evidence comparing umeclidinium 62.5 mcg with other long-acting monotherapy treatments. Consequently, there were no long-term (> 24 weeks) efficacy or safety data, and there were limitations in the interpretability of longer-term outcomes that are meaningful to patients, such as frequency of exacerbations, disease progression, and survival.

Efficacy

In the 24-week parallel-group study (DB2113373), one death occurred in the placebo group (post-treatment due to painful lymph nodes in the neck); and three deaths occurred in the umeclidinium 62.5 mcg group (two post-treatment and one on-treatment). The on-treatment death in the umeclidinium 62.5 mcg group was due to COPD and acute respiratory failure. No deaths were reported in the 12-week parallel-group study (AC4115408) or the two exercise endurance studies (DB2114417 and DB2114418). One study assessed health care resource utilization (DB2113373) and reported a low percentage of patients with health care resource use. There was a small percentage difference of 0.8% and 1% between placebo and umeclidinium 62.5 mcg groups for the proportion of patients with emergency department visits and hospital admissions, respectively. The meaningfulness of mortality and health care resource utilization data was limited due to the short duration of trials and the characteristics of the selected patient population.

The frequency of COPD exacerbations is an important efficacy outcome in interventional studies for patients with COPD, particularly the events that lead to emergency room visits or hospitalizations. The percentage of patients experiencing a COPD exacerbation was higher in the placebo groups compared with the umeclidinium 62.5 mcg groups in all four studies. A higher percentage of patients experienced severe consequences from COPD exacerbations in the umeclidinium 62.5 mcg group than in the placebo group in the 24-week efficacy study (DB2113373), with a higher percentage of patients visiting the emergency room (4.5% versus 2.9%) and/or being hospitalized (3.3% versus 1.1%) due to an

exacerbation. European Medicines Agency (EMA) guidance suggests a one-year study period for evaluating COPD exacerbations,[2] so the 12-week and 24-week durations of the included trials are not likely to provide enough time for meaningful conclusions to be drawn between treatment groups.

Change from baseline in trough FEV_1 was the primary or co-primary end point in all four included studies. There was a statistically significant increase in trough FEV_1 from baseline to end of treatment across each of the four studies (least squares [LS] mean changes versus placebo were: AC4115408: 0.13 L [95% CI, 0.05 to 0.20]; DB2113373: 0.12 L [95% CI, 0.08 to 0.16]; DB2114417: 0.09 L [95% CI, 0.03 to 0.14]; DB2114418: 0.14 L [95% CI, 0.09 to 0.20]). The results exceeded the minimal clinically important difference (MCID) of 0.10 L in all studies except for one exercise endurance study (DB2114417).

Lung volumes (trough IC, trough FRC, and trough RV) were assessed in the exercise endurance studies. Results from these assessments were generally suggestive of improvement with the use of umeclidinium 62.5 mcg compared with placebo. Statistically significant improvements in trough FRC were found for the umeclidinium 62.5 mcg group versus placebo in study DB2114417 (LS mean change from baseline versus placebo: –0.28 L [95% CI, –0.48 to –0.09]), but not in study DB2114418 (LS mean change from baseline versus placebo: –0.12 L [95% CI, –0.29 to 0.06]). For trough RV, the adjusted mean change from baseline versus placebo reached statistical significance in both studies (LS mean change versus placebo in DB2114417: –0.38 L [95 % CI, –0.58, –0.17; P <0.001] and in DB2114418: –0.22 L [95% CI, –0.40 to –0.03; P = 0.02]). The adjusted mean change from baseline for trough IC in the umeclidinium 62.5 mcg group versus placebo did not reach statistical significance in either study (LS mean change versus placebo in DB2114417: 0.03 L [95% CI, –0.07 to 0.13; P = 0.59] and in DB2114418: 0.10 L [95% CI, –0.01 to 0.20; P = 0.06]).

For the measures of dyspnea, differences in the TDI and EDS scores met the threshold of clinical importance (threshold of 1.0 unit) for the 12-week and 24-week parallel-group studies (LS mean versus placebo in AC4115408: 1.0 [95% CI, 0.0 to 2.0] and in DB2113373: 1.0 [95% CI, 0.5 to 1.5]). There were no statistically significant or clinically important changes in dyspnea scores in the exercise endurance studies (DB2114417 and DB2114418). There was a large numerical drop (LS mean change: –0.3) in dyspnea scores in the placebo group of one exercise endurance study (DB2114417).

Health-related quality of life (HRQoL) was assessed using the SGRQ in the 12-week and 24-week parallel-group studies (AC4115408 and DB2113373). There was a statistically significant and clinically important improvement in SGRQ total scores for the umeclidinium 62.5 mcg group versus placebo in both studies. There was a numerically lower LS mean change in SGRQ total score for the umeclidinium 62.5 mcg group compared with placebo in the 24-week parallel-group study compared with the 12-week parallel-group study (AC4115408: –7.9 [95% CI, –12.2 to –3.6]; DB2113373: –4.7 [95% CI, –7.1 to –2.3], respectively). Higher scores are indicative of greater impairment, and a change from baseline of four units is considered clinically meaningful.

There were no statistically significant or clinically important differences between the umeclidinium 62.5 mcg groups and placebo groups in three-hour post-dose EET at week 12 in either exercise endurance study (LS mean change versus placebo in DB2114417: 26.5 [95% CI, –25.9 to 78.9] and in DB2114418: 25.0 [95% CI, –41.0 to 91.0]). EET and lung volumes are likely to be better correlated with activity tolerance for patients with COPD compared with FEV_1; however, the exercise endurance studies that measure these outcomes suffer from several limitations. It is possible that the studies were underpowered to detect change in EET for the comparison between umeclidinium 62.5 mcg and

placebo. A priori sample-size calculations indicated that with the anticipated sample size, there would be 64% power to detect differences between groups. Regardless of the power concerns, no clinically important difference was found between umeclidinium 62.5 mcg and placebo on the EET. The exercise endurance studies were further limited by their short durations and the inclusion of a high percentage of current smokers. It is possible that the trials were not long enough to appropriately assess measures of hyperinflation, and the high percentage of smokers (61% and 63%) may have lessened patients' overall treatment responsiveness. The numerical and statistical differences in results between the two studies also make interpretation of the results difficult and any overall conclusions less definitive.

There was no direct evidence available to assess the efficacy of umeclidinium 62.5 mcg versus other long-acting monotherapy treatments in the included studies. The manufacturer submitted an indirect treatment comparison (ITC) to compare the efficacy and safety of umeclidinium 62.5 mcg to tiotropium 18 mcg, aclidinium 400 mcg, and glycopyrronium 50 mcg for the treatment of COPD. Comparative efficacy was based on a measure of trough FEV_1, SGRQ total score, TDI focal score, and rescue medication use at weeks 12 and 24. There were 24 placebo-controlled studies included in the ITC; no head-to-head trials were identified. The results of the ITC suggested that there is no statistically or clinically significant difference in outcomes between umeclidinium 62.5 mcg and tiotropium 18 mcg, aclidinium 400 mcg, and glycopyrronium 50 mcg. The substantial degree of clinical heterogeneity identified between the included studies is an important limitation because the validity of indirect comparisons rests on a sufficient degree of comparability in methods, populations, and outcome definitions across studies (APPENDIX 5). The comparative efficacy of umeclidinium 62.5 mcg in reducing the frequency of COPD exacerbations and improving exercise tolerance is unknown.

Harms

Umeclidinium 62.5 mcg was generally well tolerated by patients across studies and treatment groups. The 24-week parallel-group study (DB2113373) was the longest of the four included studies and had the highest proportion of patients experiencing an adverse event (AE), serious adverse event (SAE), withdrawal due to adverse event (WDAE), or notable harm. The proportion of patients experiencing an AE varied across trials, ranging from 12% in the umeclidinium 62.5 mcg group of study DB2114417 to 52% in the umeclidinium 62.5 mcg group of study DB2113373. The most common AEs across all trials were headache and nasopharyngitis. Across treatment groups, the proportion of patients experiencing SAEs or WDAEs ranged from 0% to 6% and 0% to 8%, respectively. Within studies, cardiovascular events were generally similar between the umeclidinium 62.5 mcg and placebo groups, and anticholinergic effects and cases of pneumonia were uncommon (≤ 4% of patients within treatment groups).

It is possible that the high percentage of patients discontinuing treatment and the disproportionately higher number of patients discontinuing in the placebo group compared with the umeclidinium 62.5 mcg group of most studies (except study DB2114417, where the percentage of patients who discontinued was 14% in both groups) may have biased the harms data that emerged from the included studies. The high rate of discontinuations may also have resulted in an underestimation of the rate of anticholinergic effects experienced by the umeclidinium 62.5 mcg groups. The higher rate of anticholinergic effects in the placebo group compared with the rate in the umeclidinium group is both surprising and counter-intuitive given the side effects associated with LAMAs. The manifestation of some AEs, such as cardiovascular effects and pneumonia, may take time to materialize; the short duration of the included studies makes it difficult to draw convincing conclusions for these outcomes.

Conclusions

Six manufacturer-sponsored trials met the inclusion criteria for this review. Two double-blind, randomized parallel-group trials and two double-blind, randomized crossover studies were summarized in this review. Overall, the strength of the evidence was limited for several key efficacy outcomes of interest — including mortality, health care resource utilization, and COPD exacerbations — due to the short study durations. There were statistically significant gains in lung function as measured by the primary efficacy end point of the included studies — trough FEV_1 — after 12 weeks and 24 weeks of treatment with umeclidinium 62.5 mcg, and clinically significant improvements in all but one study. The exercise endurance studies evaluated outcomes of particular clinical importance to patients; however, given the short duration of trials and the variability in results between seemingly similarly conducted trials, the interpretation of results was difficult, and overall conclusions were less definitive. In light of these limitations, there were improvements in lung volume and air trapping measures (trough FRC and RV) among patients taking umeclidinium 62.5 mcg, but no statistically significant improvements in EET. SAEs and WDAEs were generally low, with no consistently observable differences between umeclidinium 62.5 mcg and placebo treatment groups across trials. Umeclidinium 62.5 mcg was generally well tolerated by patients with respect to cardiovascular effects, anticholinergic effects, and cases of pneumonia; however, no long-term data were available. Indirect evidence suggested no difference in the comparative efficacy of umeclidinium 62.5 mcg versus other LAMAs. There was no direct or indirect evidence available to assess the comparative safety of umeclidinium 62.5 mcg versus other long-acting monotherapy treatments.

TABLE 1: SUMMARY OF RESULTS (12-WEEK AND 24-WEEK PARALLEL-GROUP STUDIES)

Outcome	AC4115408		DB2113373	
	PBO	UMEC 62.5 mcg	PBO	UMEC 62.5 mcg
N	**68**	**69**	**280**	**418**
Efficacy				
Deaths, n (%)	0	0	1[a]	3[a]
Health Care Resource Utilization, n (%)[b]				
Emergency room or urgent care	NA	NA	3 (1.1)	8 (1.9)
Admitted to hospital	NA	NA	1 (0.4)	6 (1.4)
COPD Exacerbation, n (%)[b]	7 (10.3)	5 (7.2)	35 (12.5)	33 (7.9)
Trough FEV_1 (L)				
LS mean (SE)	1.24 (0.03)	1.36 (0.03)	1.24 (0.02)	1.35 (0.01)
LS MC (SE)	–0.007 (0.03)	0.12 (0.03)	0.004 (0.02)	0.12 (0.01)
LS MC vs. PBO (95% CI)[c]	NA	0.13 (0.05 to 0.20)[d]	NA	0.12 (0.08 to 0.16)[d]
TDI Focal Score				
LS mean (SE)	–0.3 (0.38)	0.7 (0.34)	1.2 (0.20)	2.2 (0.16)
LS mean vs. PBO (95% CI)[e]	NA	1.0 (0.0, 2.0)	NA	1.0 (0.5 to 1.5)[d]
SGRQ Total Score				
Baseline mean (SD)	46.4 (17.9)	45.9 (16.4)	51.3 (18.1)	48.8 (18.2)
LS mean (SE)	50.3 (1.6)	42.4 (1.5)	46.6 (1.0)	41.9 (0.8)
LS MC (SE)	4.8 (1.6)	–3.1 (1.5)	–2.6 (1.0)	–7.3 (0.8)
LS MC vs. PBO (95% CI)[f]	NA	–7.9 (–12.2 to –3.6)[d]	NA	–4.7 (–7.1 to –2.3)[d]
Harms				
AEs, n (%)	24 (35)	27 (39)	130 (46)	216 (52)
SAEs, n (%)	1 (1)	1 (1)	9 (3)	27 (6)
WDAEs, n (%)	0	1 (1)	9 (3)	34 (8)
Notable Harms, n (%)				
Cardiovascular	1 (1)	2 (3)	26 (9)	41 (10)
Anticholinergic	3 (4)	0	8 (3)	18 (4)
Pneumonia	0	0	2 (< 1)	6 (1)

AE = adverse event; CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second; LS = least squares; MC = mean change; N = number of patients randomized; n = number of patients; NA = not applicable; PBO = placebo; SAE = serious adverse event; SD = standard deviation; SE = standard error; SGRQ = St. George's Respiratory Questionnaire; TDI = Treatment Dyspnea Index; UMEC = umeclidinium bromide; WDAE = withdrawal due to adverse event.

[a] One death occurred on-treatment in the UMEC 62.5 mcg group (due to COPD and acute respiratory failure); all other deaths occurred post-treatment (one in the placebo group, related to painful lymph nodes in the neck; and two in the umeclidinium 62.5 mcg group: one due to sudden death and one due to cholecystitis and peritonitis).

[b] Percentage is based on the N for each treatment group as the denominator.

[c] Repeated measures analysis controlling for: treatment, baseline (FEV_1 pre-dose), smoking status, centre group, day, day × baseline, day × treatment.

[d] $P < 0.05$.

[e] Repeated measures analysis controlling for: treatment, baseline (SGRQ pre-dose day 1), smoking status, centre group, day, day × baseline, day × treatment.

Source: Manufacturer-submitted Clinical Study Reports.[3,4]

TABLE 2: SUMMARY OF RESULTS (EXERCISE ENDURANCE STUDIES)

Outcome	DB2114417		DB2114418	
	PBO	UMEC 62.5 mcg	PBO	UMEC 62.5 mcg
N	**170**	**49**	**151**	**40**
Efficacy				
Deaths, n (%)	0	0	0	0
COPD Exacerbation, n (%)[a]	11 (6.5)	1 (2.0)	16 (10.6)	0
3-Hour Post-dose EET (seconds)				
Baseline mean (SD)	316.1 (171.8)	280.5 (152.7)	339.7 (193.0)	318.0 (167.0)
LS MC (SE)	36.7 (13.2)	63.2 (23.9)	0.1 (16.7)	25.1 (30.2)
LS MC vs. PBO (95% CI)[b]	NA	26.5 (–25.9 to 78.9)	NA	25.0 (–41.0 to 91.0)
Trough FEV_1				
LS mean (SE)	1.40 (0.01)	1.49 (0.03)	1.28 (0.02)	1.42 (0.03)
LS MC (SE)	–0.03 (0.02)	0.05 (0.03)	–0.04 (0.02)	0.10 (0.03)
LS MC vs. PBO (95% CI)[a]	NA	0.09 (0.03 to 0.14)[c]	NA	0.14 (0.09 to 0.20)[c]
Trough IC (L)				
Baseline mean (SD)	2.26 (0.61)	2.28 (0.49)	2.14 (0.7)	2.14 (0.6)
LS mean (SE)	2.26 (0.03)	2.28 (0.05)	2.15 (0.03)	2.24 (0.05)
LS MC (SE)	–0.002 (0.03)	0.03 (0.05)	–0.02 (0.03)	0.08 (0.05)
LS MC vs. PBO (95% CI)[a]	NA	0.03 (–0.07 to 0.13)	NA	0.10 (–0.01 to 0.20)
Trough FRC (L)				
Baseline mean (SD)	4.76 (1.26)	4.85 (1.28)	4.87 (1.37)	4.75 (1.05)
LS mean (SE)	4.80 (0.05)	4.47 (0.09)	4.72 (0.05)	4.60 (0.08)
LS MC (SE)	0.02 (0.05)	–0.26 (0.09)	–0.08 (0.05)	–0.20 (0.08)
LS MC vs. PBO (95% CI)[a]	NA	–0.28 (–0.48 to –0.09)[c]	NA	–0.12 (–0.29 to 0.06)
Trough RV (L)				
Baseline mean (SD)	4.05 (1.17)	4.10 (1.26)	4.01 (1.27)	3.82 (1.01)
LS mean (SE)	4.05 (0.05)	3.68 (0.09)	3.91 (0.05)	3.69 (0.08)
LS MC (SE)	0.04 (0.05)	–0.34 (0.09)	–0.05 (0.05)	–0.27 (0.08)
LS MC vs. PBO (95% CI)[a]	NA	–0.38 (–0.58 to –0.17)[c]	NA	–0.22 (–0.40 to –0.03)[c]
EDS (at iso-time)				
LS mean (SE)	3.7 (0.1)	3.5 (0.2)	3.3 (0.11)	3.0 (0.21)
LS MC (SE)	–0.3 (0.1)	–0.5 (0.2)	–0.01 (0.11)	–0.33 (0.21)
LS MC vs. PBO (95% CI)[d]	NA	–0.2 (–0.6 to 0.3)	NA	–0.32 (–0.78 to 0.13)
Harms				
AEs, n (%)	46 (27)	6 (12)	59 (39)	12 (30)
SAEs, n (%)	6 (4)	0	4 (3)	1 (3)
WDAEs, n (%)	9 (5)	2 (4)	8 (5)	1 (3)

Outcome	DB2114417		DB2114418	
	PBO	UMEC 62.5 mcg	PBO	UMEC 62.5 mcg
N	**170**	**49**	**151**	**40**
Notable Harms, n (%)				
Cardiovascular	6 (4)	1 (2)	2 (1)	1 (3)
Anticholinergic	2 (1)	0	6 (4)	0
Pneumonia	1 (< 1)	1 (2)	2 (1)	0

AE = adverse event; CI = confidence interval; COPD = chronic obstructive pulmonary disease; EDS = Exercise Dyspnea Scale; EET = exercise endurance time; FEV_1 = forced expiratory volume in one second; FRC = functional residual capacity; IC = inspiratory capacity; iso-time = the time point that the individual patient's baseline walking time was taken; LS = least squares; MC = mean change; N = number of patients randomized; n = number of patients; NA = not applicable; PBO = placebo; RV = residual volume; SAE = serious adverse event; SD = standard deviation; SE = standard error; UMEC = umeclidinium bromide; WDAE = withdrawal due to adverse event.

[a] Repeated measures analysis controlling for: period baseline, mean baseline, period, treatment, visit, smoking status, centre group, visit × period, visit × mean baseline, visit × treatment.

[b] Repeated measures analysis controlling for: period walking speed, mean walking speed, period, treatment, visit, smoking status, centre group, visit × period walking speed, visit × mean walking speed and visit × treatment.

[c] $P < 0.05$.

[d] Repeated measures analysis controlling for: period baseline, mean baseline, period, treatment, visit, smoking status, centre group, visit × period baseline, visit × mean baseline and visit × treatment.

Source: Manufacturer-submitted Clinical Study Reports.[5,6]

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.[7,8] Pathological changes in the lung vary between individuals, but usually involve a combination of airway inflammation (chronic bronchitis) and parenchymal destruction (emphysema).[9] Patients' everyday lives are affected, including their ability to breathe, talk, sleep, work, and socialize. Many individuals present with features of both chronic bronchitis and emphysema, as well as asthma, which differs fundamentally from COPD.[8] COPD is largely caused by smoking, and is associated with multiple comorbid conditions (e.g., diabetes, ischemic heart disease, muscle wasting, bone loss, anemia, cancer, anxiety, and depression).[8]

COPD is a major public health problem and a leading cause of morbidity and mortality worldwide, associated with an economic and social burden that is both substantial and increasing.[10] By 2020, COPD is projected to become the third leading cause of death worldwide.[10]

According to a 2009 Statistics Canada report, COPD affects 4% of the Canadian population aged 35 years and older.[11] Among COPD patients in Canada aged 35 years to 79 years, 7% had stage II (moderate) or higher COPD.[12] COPD is associated with an increased risk of mortality, and was ranked as the fourth leading cause of death in Canada in 2004.[7] COPD is associated with high rates of admissions and readmissions to hospital (e.g., of all COPD patients hospitalized in 2006 and 2007, 18% were readmitted once and 14% were readmitted twice).[13] Hospital admissions for COPD exacerbations averaged a 10-day length of stay at a cost of $10,000 per stay. The total cost of COPD hospitalizations in Canada is estimated at $1.5 billion per year.[14]

Diagnosing and determining the severity of COPD typically requires the use of spirometry. The two indicators necessary for establishing a diagnosis of COPD are forced expiratory volume in one second (FEV_1), which is the amount of air that one can expel in one second, and forced vital capacity (FVC), which is the amount of air that one can expel upon full inspiration with no limit to duration of expiration. A post-bronchodilator FEV_1/FVC ratio < 0.7 indicates airway obstruction. The Canadian Thoracic Society (CTS) classification of COPD severity is summarized in Table 3.

TABLE 3: CANADIAN THORACIC SOCIETY CLASSIFICATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE SEVERITY BY SYMPTOMS, DISABILITY, AND LUNG FUNCTION IMPAIRMENT

COPD Stage	Spirometry (Post-bronchodilator)	Symptoms
I: Mild	$FEV_1 \geq 80\%$ predicted; $FEV_1/FVC < 0.7$	Shortness of breath from COPD[a] when hurrying on the level or walking up a slight hill (MRC 2)
II: Moderate	$50\% \leq FEV_1 < 80\%$ predicted; $FEV_1/FVC < 0.7$	Shortness of breath from COPD[a] causing the patient to stop after walking approximately 100 m (or after a few minutes) on the level (MRC 3 to 4)
III: Severe	$30\% \leq FEV_1 < 50\%$ predicted; $FEV_1/FVC < 0.7$	Shortness of breath from COPD[a] resulting in the patient being too breathless to leave the house, breathless when dressing or undressing (MRC 5), 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; MRC = Medical Research Council dyspnea scale; NR = not reported.
[a] In the presence of non-COPD conditions that may cause shortness of breath (e.g., cardiac dysfunction, anemia, muscle weakness, metabolic disorders), symptoms may not appropriately reflect COPD disease severity. Classification of COPD severity should be undertaken with care in patients with comorbid diseases or other possible contributors to shortness of breath.
Note: A post-bronchodilator FEV_1 to FVC ratio of < 0.7 is required to establish the diagnosis of COPD.
Source: Adapted from: O'Donnell et al. 2007.[7]

1.2 Standards of therapy

The goals of COPD management are to prevent disease progression, reduce frequency and severity of exacerbations, alleviate symptoms, improve exercise tolerance and ability to perform daily activities, treat exacerbations and complications, improve health status, and reduce mortality.[7] Exacerbations are a concern for patients, as they are associated with both short- and long-term consequences on overall health. Management decisions are guided by disease severity (i.e., symptoms, disability, and spirometry) and the frequency of acute exacerbations.

Smoking cessation is the single most effective intervention to reduce the risk of developing COPD, and is the only intervention shown to slow the rate of lung function decline.[8] Regular exercise with cardiorespiratory conditioning can improve functional status and sensation of dyspnea in patients with COPD, more so than the use of medications alone.

Pharmacotherapy for COPD also follows a stepwise approach driven by severity of disease and the frequency of acute exacerbations. Inhaled bronchodilators are the mainstay of treatment for COPD,[8] and include short-acting beta2-agonists (SABAs), such as salbutamol, and short-acting muscarinic antagonists (SAMAs), such as ipratropium. The most commonly used treatments for COPD in Canada are: long-acting beta2-agonists (LABAs), such as salmeterol, formoterol, and indacaterol; or long-acting muscarinic antagonists (LAMAs), such as tiotropium, aclidinium, and glycopyrronium (Table 4); as well as fixed-dose dual bronchodilators (LAMAs/LABAs), such as indacaterol/glycopyrronium (Ultibro) and umeclidinium/vilanterol (Anoro); and fixed-dose LABAs and inhaled corticosteroids (ICSs) (i.e., LABA/ICS), such as fluticasone/salmeterol (Advair) or budesonide/formoterol (Symbicort).

Muscarinic antagonists and beta2-agonists are often used in combination for maximal improvement in dyspnea and function. Fixed-dose LABA/ICSs may not be useful for mild disease; however, they may

have more of a role in the management of patients with a history of exacerbations and moderate to severe COPD, or in those with persistent symptoms.[15-17] There may also be a subpopulation of COPD patients who have concomitant asthma or airway eosinophilia, in whom ICS use may be beneficial.[18-20] Phosphodiesterase inhibitors (theophylline, and more recently, roflumilast) are adjunctive therapies for COPD management. Inhaled medications are most commonly delivered as pressurized metered-dose inhalers and dry powder inhalers. Incorrect use of inhalers is a constant challenge in COPD (APPENDIX 1).

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.[8]

1.3 Drug

Umeclidinium bromide is a LAMA that acts through muscarinic receptors of the smooth muscle cells of the airway. It competitively inhibits the binding of acetylcholine to the muscarinic receptor subtypes M_1 to M_5 to produce bronchodilation. It has a slow reversibility to the M_3 receptor subtype and exerts its effects over a 24-hour period. It is approved for use in Canada as a long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including those with chronic bronchitis and emphysema. The recommended dose is 62.5 mcg once daily administered as a dry powder, oral inhalation using the Ellipta device. It is not indicated for use as a rescue therapy (i.e., for acute bronchospasms).[21] Umeclidinium is also available in Canada combined with vilanterol in the LAMA plus LABA fixed-dose combination, Anoro Ellipta.

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 other LAMAs as a maintenance bronchodilator treatment for COPD.

TABLE 4: KEY CHARACTERISTICS OF UMECLIDINIUM BROMIDE, TIOTROPIUM BROMIDE, ACLIDINIUM BROMIDE, AND GLYCOPYRRONIUM BROMIDE

	Umeclidinium Bromide	Tiotropium Bromide	Aclidinium Bromide	Glycopyrronium Bromide
Mechanism of Action	LAMA with high affinity across multiple muscarinic receptor subtypes and a slow reversibility from M3	LAMA with a similar affinity to muscarinic receptors M1 to M5 and slow dissociation kinetics from M3	LAMA with similar affinity to muscarinic receptors M1 to M5 and a kinetic preference for M3	LAMA with a high affinity for muscarinic receptors M1, M2, and M3
Indication[a]	Long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema	Respimat: Long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema, and for the reduction of exacerbations HandiHaler: Long-term, once-daily maintenance treatment of bronchospasm associated with COPD, including bronchitis and emphysema	Long-term maintenance bronchodilator treatment in patients with COPD, including bronchitis and emphysema	Long-term, once-daily maintenance bronchodilator treatment in adult patients with COPD, including chronic bronchitis and emphysema
Route of Administration	Oral inhalation using the Ellipta device	Oral inhalation using the Respimat or HandiHaler device	Oral inhalation using the Genuair device	Oral inhalation using the Breezhaler device
Recommended Dose	62.5 mcg once daily	Respimat: 2 × 2.5 mcg once daily HandiHaler: 18 mcg once daily	400 mcg twice daily (once in the morning and once in the evening)	50 mcg once daily
Serious Side Effects/Safety Issues	Anticholinergic (i.e., use with caution in patients with narrow-angle glaucoma or urinary retention) and cardiovascular effects	Anticholinergic (i.e., use with caution in patients with narrow-angle glaucoma, prostatic hyperplasia, or bladder-neck obstruction) and cardiovascular effects	Anticholinergic (i.e., use with caution in patients with narrow-angle glaucoma or urinary retention) and cardiovascular effects	Anticholinergic effects (i.e., use with caution in patients with narrow-angle glaucoma or urinary retention) and cardiovascular effects

	Umeclidinium Bromide	Tiotropium Bromide	Aclidinium Bromide	Glycopyrronium Bromide
Other	Single-dose; dry powder	Respimat: multi-dose; soft-mist HandiHaler: single-dose; dry powder	Multi-dose; dry powder	Single-dose; dry powder

COPD = chronic obstructive pulmonary disease; LAMA = Long-acting muscarinic antagonist.
[a] Health Canada indication.
Source: Product Monographs: Incruse Ellipta,[21] Spiriva Respimat,[22] Spiriva HandiHaler,[23] Tudorza Genuair,[24] Seebri Breezhaler.[25]

2. OBJECTIVES AND METHODS

2.1 Objective

To perform a systematic review of the beneficial and harmful effects of umeclidinium bromide (Incruse) 62.5 mcg delivered via the Ellipta dry powder inhaler (DPI) for the long-term maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema.

2.2 Methods

Studies selected for inclusion in the systematic review included the pivotal studies provided in the manufacturer's submission to the CADTH Common Drug Review (CDR) as well as those meeting the selection criteria presented in Table 5.

TABLE 5: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult patients (≥ 18 years) with COPD, including chronic bronchitis and emphysema **Subgroups**: Age, sex, BMI, COPD severity, bronchodilator reversibility, chronic bronchitis, emphysema, smoking status, concomitant cardiovascular disease, background inhaled medication
Intervention	Umeclidinium bromide 62.5 mcg administered once daily via a dry powder inhaler
Comparators	The following comparators used alone or in combination (as appropriate): • SABA (e.g., salbutamol) • SAMA (e.g., ipratropium) • LABA (e.g., salmeterol, formoterol, indacaterol) • LAMA (e.g., tiotropium, aclidinium, glycopyrronium) • ICS (in combination only, e.g., ICS/LABA) • PDE-4 inhibitors (e.g., roflumilast) • Theophylline
Outcomes	**Key efficacy outcomes:** • Mortality (i.e., all-cause and COPD-related) • Health care resource utilization (e.g., hospitalizations, emergency room visits) • COPD exacerbations • Pulmonary function tests (e.g., spirometric measures: FEV_1) • Symptoms (i.e., day and night, including dyspnea) • Health-related quality of life (e.g., SGRQ) • Function and disability (e.g., MRC dyspnea score) • Exercise tolerance (e.g., TLC, RV, IC)

	Other efficacy outcomes: • Use of rescue medication • Patient adherence and satisfaction • Days of missed work or school **Harms outcomes:** • AEs • SAEs • WDAEs • AEs of special interest: cardiovascular-related, pneumonia, anticholinergic
Study Design	Published and unpublished phase 3 RCTs

AEs = adverse events; BMI = body mass index; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second; IC = inspiratory capacity; ICS = inhaled corticosteroids; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; MRC = Medical Research Council; PDE4 = phosphodiesterase 4; RCT = randomized controlled trial; RV = residual volume; SABA = short-acting beta2-agonist; SAE = serious adverse event; SAMA = short-acting muscarinic antagonist; SGRQ = St. George's Respiratory Questionnaire; TLC = total lung capacity; WDAE = withdrawal due to adverse event.

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

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

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

The initial search was completed on March 27, 2015. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) in August 2015. Regular search updates were performed on databases that do not provide alert services.

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

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 6 and Table 7; excluded studies (with reasons) are presented in APPENDIX 3.

3. RESULTS

3.1 Findings from the literature

A total of six studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 6 and Table 7 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

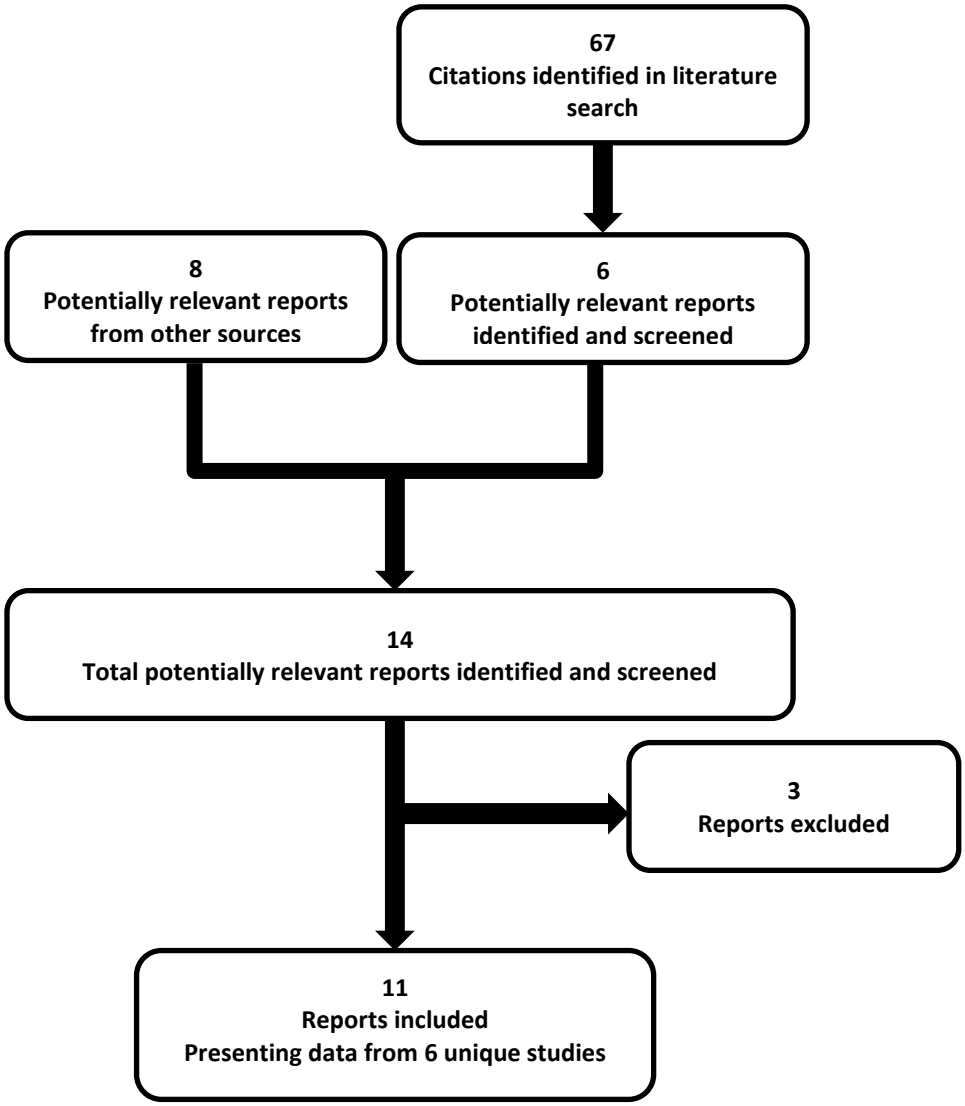

TABLE 6: DETAILS OF INCLUDED STUDIES

		AC4115408	DB2113373	DB2114417	DB2114418
DESIGNS & POPULATIONS	**Study Design**	DB RCT	DB RCT	DB RCT crossover	DB RCT crossover
	Locations	USA, Germany, Japan	Canada, USA, Japan, Russia, Europe, Chile, South Africa, Mexico, Thailand	USA, Russia, Europe	Canada, USA, Europe, South Africa
	Randomized (N)	206	1,536	349	308
	Inclusion Criteria	• Outpatient • Age ≥ 40 years • Clinical history of COPD • Current or former cigarette smoker[a] (≥ 10 pack-years) • Post-salbutamol FEV_1/FVC < 0.70 and FEV_1 ≤ 70% • mMRC ≥ 2		• Outpatient • Age ≥ 40 years • Clinical history of COPD • Current or former cigarette smoker[a] (≥ 10 pack-years) • Post-salbutamol FEV_1/FVC < 0.70 and FEV_1 ≥ 35% and ≤ 70% • mMRC ≥ 2 • Resting FRC ≥ 120%	
	Exclusion Criteria	• Diagnosis of asthma • History or current evidence of clinically significant[b] cardiovascular or endocrine abnormalities • Hospitalization for COPD or pneumonia within 12 weeks • Lung reduction surgery within 12 months • Long-term oxygen therapy (> 12 hours/day) • Daily use of short-acting bronchodilators • Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks • Previous use of UMEC or UMEC/VI		• Diagnosis of asthma • History or current evidence for clinically significant[b] cardiovascular or endocrine abnormalities • Hospitalization for COPD or pneumonia within 12 weeks • Lung reduction surgery within 12 months • Long-term oxygen therapy (> 12 hours/day) • Daily use of short-acting bronchodilators • Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks	
DRUGS	**Intervention**	UMEC 62.5 mcg q.d. DPI			
	Comparator(s)	Placebo UMEC 125 mcg q.d. DPI[c]	Placebo UMEC 62.5 mcg/ VI 25 mcg q.d. DPI[d] VI 25 mcg q.d. DPI[c]	Placebo UMEC 62.5 mcg/VI 25 mcg q.d. DPI[d] UMEC 125 mcg/VI 25 mcg q.d. DPI[c] UMEC 125 mcg q.d. DPI[c] VI 25 mcg q.d. DPI[c]	
DURATION	**Phase**				
	Run-in	5 to 9 days	7 to 14 days	12 to 21 days	
	Double-blind	12 weeks	24 weeks	12 weeks × 2[e]	
	Follow-up	1 week			
OUTCOMES	**Primary End Point**	Trough FEV_1[f]		3-hour post-dose EET[g]/trough FEV_1[f]	
	Other End Points	Other spirometry measures, dyspnea, rescue salbutamol use,	Other spirometry measures, dyspnea, rescue salbutamol use, quality of life, health	Other spirometry measures, dyspnea, rescue salbutamol use, COPD exacerbation, harms	

		AC4115408	DB2113373	DB2114417	DB2114418
		quality of life, COPD exacerbation, harms	care resource utilization, COPD exacerbation, harms		
NOTES	**Publications**	Trivedi et al. 2014[26]	Donohue et al. 2013[27]	Maltais et al. 2014[28]	

COPD = chronic obstructive pulmonary disease; DB = double-blind; DPI = dry powder inhaler; EDS = Exercise Dyspnea Scale; EET = exercise endurance test; FEV_1 = forced expiratory volume in one second; FRC = functional residual capacity; FVC = forced vital capacity; mMRC = modified Medical Research Council dyspnea scale; N = number of patients; q.d. = once daily; RCT = randomized controlled trial; UMEC = umeclidinium; VI = vilanterol.

[a] Former cigarette smokers were defined as those who had stopped smoking at least 6 months ago.

[b] Clinically significant was defined as a condition that would put the patient at risk or would have affected the efficacy or safety analysis of the study.

[c] Comparator arm not approved by Health Canada.

[d] Data for comparator arm presented in the CADTH Common Drug Review Anoro Ellipta clinical review report.[1]

[e] Patients were randomized to a set of two 12-week treatment periods separated by a two-week washout period.

[f] Mean change from baseline to day 85 (AC4115408, DB2114417, DB2114418) or day 169 (DB2113373) in trough FEV_1 (taken as the mean FEV_1 obtained 23 and 24 hours after last dose).

[g] Mean change from baseline to day 85.

Note: Two additional reports were included.[29,30]

Source: Manufacturer-submitted Clinical Study Reports.[3-6]

TABLE 7: DETAILS OF INCLUDED STUDIES (CONTINUED)

		DB2116132	DB2116133
DESIGNS & POPULATIONS	**Study Design**	DB RCT crossover	
	Locations	Europe	
	Randomized (N)	207	182
	Inclusion Criteria	• Outpatient • Age ≥ 40 years • Clinical history of COPD • Current or former cigarette smoker[a] (≥ 10 pack-years) • Post-salbutamol FEV_1/FVC < 0.70 and FEV_1 ≤ 70%	
	Exclusion Criteria	• Diagnosis of asthma • History or current evidence of clinically significant[b] cardiovascular or endocrine abnormalities • Hospitalization for COPD or pneumonia within 12 weeks • Lung reduction surgery within 12 months • Long-term oxygen therapy (> 12 hours/day) • Daily use of short-acting bronchodilators • Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks	
DRUGS	**Intervention**	UMEC 62.5 mcg q.d. DPI	
	Comparator(s)	VI 25 mcg q.d. DPI UMEC 62.5 mcg/VI 25 mcg q.d. DPI	
DURATION	**Phase**		
	Run-in	5 to 7 days	
	Double-blind	2 weeks × 3[c]	
	Follow-up	7 to 9 days	
OUTCOMES	**Primary End Point**	0- to 6-hour post-dose weighted mean FEV_1	
	Other End Points	Response,[d] other spirometry measures, rescue salbutamol use, COPD exacerbation, harms	
NOTES	**Publications**	None	

COPD = chronic obstructive pulmonary disease; DB = double-blind; DPI = dry powder inhaler; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; N = number of patients; q.d. = once daily; RCT = randomized controlled trial; UMEC = umeclidinium; VI = vilanterol.

[a] Former cigarette smokers were defined as those who had stopped smoking for at least 6 months.

[b] Clinically significant was defined as a condition that would put the patient at risk or would have affected the efficacy or safety analysis of the study.

[c] Patients were randomized to a set of three 2-week treatment periods separated by a 10- to 14-day washout period.

[d] Proportion of patients who had an increase in FEV_1 of 12% and 200 mL during the 0- to 6-hour post-dose period.

Note: Two additional reports were included.[29,30]

Source: Manufacturer-submitted Clinical Study Reports.[31,32]

3.2 Included studies

3.2.1 Description of studies

Six superiority studies met the inclusion criteria for the review (Table 6 and Table 7). Two studies were short-term (14-day) efficacy studies using a three-way randomized crossover design. The three interventions in these short-term studies were umeclidinium 62.5 mcg, umeclidinium/vilanterol 62.5 mcg/25 mcg, and vilanterol 25 mcg; and the primary efficacy outcome was weighted mean FEV_1 zero to six hours post-bronchodilator. Due to a number of methodological issues with these studies, the details of the two short-term efficacy studies (DB2116132 and DB2116133) are limited to presentation in Section 3.1 and Section 3.2.1 of this report.

The four remaining studies were randomized, double-blinded (patient and physician), and placebo-controlled. All trials included a run-in period (lasting five to nine days for study AC4115408, seven to 14 days for DB2113373, and 12 to 21 days for the exercise endurance trials) to assess the criteria that were necessary for randomization (i.e., no COPD exacerbations, maintenance of regular ICS dose if applicable, and no use of prohibited medications). Two studies assessed the safety and efficacy of umeclidinium 62.5 mcg over a 12-week (AC4115408) and 24-week (DB2113373) period with a parallel-group randomized controlled trial (RCT) design, and two studies were exercise endurance trials (DB2114417 and DB2114418) that assessed umeclidinium 62.5 mcg with a randomized crossover design of two 12-week treatment periods separated by a 14-day washout period (Table 6 and Table 7).

In the 12-week parallel-group study (AC4115408), patients were randomized in a 1:1:1 ratio to umeclidinium 62.5 mcg once daily, umeclidinium 125 mcg once daily or placebo once daily. In the 24-week parallel-group study (DB2113373), patients were randomized in a 3:3:3:2 ratio to umeclidinium/vilanterol 62.5/25 mcg once daily, umeclidinium 62.5 mcg once daily, vilanterol 25 mcg once daily, or placebo once daily.

The two exercise endurance studies (DB2114417 and DB2114418) were randomized crossover studies where patients were randomized to one of 26 treatment sequences, each sequence consisting of a series of two interventions. The treatment sequences were generated from two of the following six interventions:

1. Umeclidinium/vilanterol 125 mcg/25 mcg once daily
2. Umeclidinium/vilanterol 62.5 mcg/25 mcg once daily
3. Umeclidinium 125 mcg once daily
4. Umeclidinium 62.5 mcg once daily
5. Vilanterol 25 mcg once daily
6. Placebo once daily.

The number of patients randomized to each group was unbalanced in order to optimize the power to detect differences between umeclidinium/vilanterol 125 mcg/25 mcg or umeclidinium/vilanterol 62.5 mcg/25 mcg and placebo. Each treatment period lasted 12 weeks, separated by a two-week washout period.

Randomization was not stratified in any of the included studies except for one exercise endurance study (DB2114417) where patients were stratified by the use of the Oxycon mobile system (yes or no). The Oxycon mobile system was used by a subset of patients (n = 154; 44% of patients randomized) to attain additional lung volumes and cardiorespiratory measurements during exercise.

Of note, the 24-week parallel-group study (DB2113373) and the exercise endurance studies (DB2114417 and DB2114418) included treatment groups that received the fixed-dose combination of umeclidinium/vilanterol (Anoro Ellipta). Data for these treatment groups have been reviewed previously by CDR[1] and were not presented in this report.

3.2.2 Populations

a) Inclusion and exclusion criteria

The inclusion criteria were similar across studies, including outpatients with moderate to severe COPD and aged 40 years or older. Patients in the exercise endurance studies were required to have satisfied additional lung functioning criteria (post-salbutamol $FEV_1 \geq 35\%$ and resting forced residual capacity [FRC] ≥ 120%) that were not required for inclusion in the 12-week and 24-week parallel-group studies. Exclusion criteria were generally the same across all trials, including a diagnosis of asthma, participation in the acute phase of a pulmonary rehabilitation program within four weeks, and the use of concomitant medications within the time frames listed in Table 8. Any patient who had taken any of the medications listed in the table within the specified time frame prior to visit 1 was excluded from the study. The 12-week and 24-week parallel-group studies also excluded patients who had previous use of umeclidinium or umeclidinium/vilanterol.

TABLE 8: EXCLUSION CRITERIA BASED ON CONCOMITANT MEDICATION TAKEN WITHIN PRE-STUDY TIME FRAMES

Time Frame[a]	4 Hours	12 Hours	48 Hours	14 Days
Pre-study Concomitant Medication	Inhaled SABAs SAMAs SABA/ SAMAs	Oral SABAs	• Switching to an ICS from a LABA/ICS combination • Oral LABAs • Inhaled LABAs • Theophyllines • Oral leukotriene inhibitors	• PDE4 inhibitor • Tiotropium
	30 Days	**6 Weeks**	**12 Weeks**	
	• Changes to LABA/ICS or ICS (unless switching to an ICS monotherapy from a LABA/ICS combination) • ICS dose > 1,000 mcg/day • Any investigational medication	• Systemic, oral, parenteral corticosteroids • Antibiotics for a lower respiratory tract infection	• Depot corticosteroids	

ICS = inhaled corticosteroids; LABA = long-acting beta2-agonist; SABA = short-acting beta2-agonists; SAMA = short-acting anticholinergic.

[a] Time frame prior to visit 1.

Source: Manufacturer-submitted Clinical Study Reports.[3-6]

b) Baseline characteristics

Demographic and baseline characteristics of the included studies are summarized in Table 9. The patients included in the exercise endurance studies differed from the 12-week and 24-week parallel-group studies on several characteristics. The exceptions were mean age (61 to 64 years), mMRC dyspnea score (2.3 to 2.4), and pre- and post-bronchodilator lung function tests, which were similar across studies. The percentage of males was numerically lower in the exercise endurance studies (55% to 65%) compared with the 12-week and 24-week parallel studies (62% to 71%). The exercise endurance studies also had a higher percentage of current smokers (61% to 63%) compared with 50% to 54% in the 12-week and 24-week parallel-group studies. The percentages of patients with a history of COPD exacerbation requiring hospitalization in the 12 months prior to study visit 1 was highest in the 24-week parallel-group study (11% to 12%), and ranged between 4% and 8% in the placebo and umeclidinium 62.5 mcg groups in the 12-week studies. One exercise endurance study (DB2114418) had double the percentage of patients with a COPD exacerbation requiring hospitalization compared with the other exercise endurance study (DB2114417) (8% versus 4%). The percentage of patients with a diagnosis of cardiac disorder was higher in one exercise endurance study (DB2114417) (32%) compared with all other studies (20 to 22%). More than 99% of patients across all studies were classified as Global Initiative for Obstructive Lung Disease (GOLD) stage II or higher, and between 19% and 39% of patients within study groups had reversibility to salbutamol. The number of patients randomized to the placebo group and umeclidinium 62.5 mcg group was higher in the 24-week parallel-group study compared with the 12-week parallel-group study (placebo: n = 280 versus n = 68; umeclidinium 62.5 mcg n = 418 versus n = 69).

Within studies, baseline patient characteristics were generally similar between treatment groups. In the 12-week parallel-group study (AC4115408), patients in the umeclidinium 62.5 mcg group had a greater percentage of patients classified as GOLD stage IV (20%) compared with the placebo group (13%). The percentage of patients in GOLD stages II and III were also imbalanced among treatment groups. Patients in the active treatment group also had a lower percentage of patients with reversibility to salbutamol (19% versus 32%) and fewer smoking pack-years (45 versus 52) compared with the placebo group.

TABLE 9: SUMMARY OF BASELINE CHARACTERISTICS

Characteristic	AC4115408		DB2113373		DB2114417	DB2114418
	PBO	UMEC 62.5 mcg	PBO	UMEC 62.5 mcg	ITT Population	ITT Population
N	**68**	**69**	**280**	**418**	**348**	**307**
Age, mean (SD)	62.5 (8.7)	62.3 (9.5)	62.2 (9.0)	64.0 (9.2)	61.6 (8.3)	62.6 (7.9)
Male, n (%)	42 (62)	44 (64)	195 (70)	298 (71)	195 (56)	168 (55)
BMI kg/m^2, mean (SD)	28.0 (5.5)	27.6 (7.4)	26.9 (5.9)	26.5 (5.6)	27.1 (5.8)	27.0 (5.7)
Smoking history						
Current smoker, n (%)	36 (53)	37 (54)	150 (54)	207 (50)	220 (63)	186 (61)
Smoking pack-years, mean (SD)[a]	52.3 (30.2)	45.2 (21.2)	47.2 (27.2)	46.8 (27.0)	48.7 (25.3)	47.4 (24.7)
COPD severity and comorbidities						
Pre-bronchodilator FEV_1(L), mean (SD)	1.2 (0.4)	1.3 (0.6)	1.2 (0.5)	1.2 (0.5)	1.4 (0.4)	1.3 (0.4)
Post-SAL FEV_1(L), mean (SD)	1.4 (0.5)	1.4 (0.6)	1.4 (0.5)	1.3 (0.5)	1.5 (0.4)	1.5 (0.4)
Post-SAL FEV_1/FVC(L), mean (SD)	46.0 (10.7)	48.0 (11.5)	47.1 (11.5)	46.8 (11.1)	49.3 (10.2)	47.9 (10.2)
Chronic bronchitis,[b] n (%)	48 (71)	50 (72)	182 (65)	274 (66)	246 (71)	195 (64)
COPD exacerbation not requiring hospitalization, n (%)[c]	16 (24)	14 (20)	78 (28)	120 (29)	61 (18)	86 (28)
COPD exacerbation requiring hospitalization, n (%)[c]	4 (5)	5 (7)	31 (11)	51 (12)	14 (4)	24 (8)
Emphysema,[b] n (%)	46 (68)	48 (70)	173 (62)	271 (65)	226 (65)	204 (67)
GOLD Stage I, n (%)	0	0	0	0	0	2 (< 1)
GOLD Stage II, n (%)	33 (49)	25 (36)	119 (43)	191 (46)	185 (53)	158 (52)
GOLD Stage III, n (%)	26 (38)	30 (43)	133 (48)	172 (41)	163 (47)	143 (47)
GOLD Stage IV, n (%)	9 (13)	14 (20)	28 (10)	54 (13)	0	1 (< 1)
SAL reversibility, n (%)	22 (32)	13 (19)	91 (33)	121 (29)	120 (34)	118 (39)
mMRC dyspnea score, mean (SD)	2.3 (0.5)	2.3 (0.5)	2.4 (0.6)	2.4 (0.6)	2.3 (0.5)	2.3 (0.5)
Current cardiac disorder, n (%)	15 (22)	14 (20)	59 (21)	100 (24)	110 (32)	65 (21)

BMI = body mass index; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; GOLD = Global Initiative for Obstructive Lung Disease; ITT = intention-to-treat; mMRC = modified Medical Research Council dyspnea scale; N = number of patients randomized; n = number of patients; PBO = placebo; SAL = salbutamol; SD = standard deviation; UMEC = umeclidinium.

[a] Equivalent to the number of cigarettes smoked per day/20 × number of years smoked.

[b] Diagnosis was based on a clinical assessment by the study investigators.

[c] Within 12 months prior to visit 1.

Source: Manufacturer-submitted Clinical Study Reports;[3-6] manufacturer provided additional information.[33]

Pre-study medication use for the included studies is summarized in Table 10. The most commonly prescribed medications were SABAs. ICS use was highest in studies DB2113373 (51% to 55% of patients) and DB2114418 (40%) compared with studies AC40115408 (23% to 26%) and DB2114417 (28%).

TABLE 10: SUMMARY OF BASELINE MEDICATION USE (PRE-STUDY)

Characteristic	AC4115408		DB2113373		DB2114417		DB2114418	
	PBO	UMEC 62.5 mcg	PBO	UMEC 62.5 mcg	PBO	UMEC 62.5 mcg	PBO	UMEC 62.5 mcg
N	**68**	**69**	**280**	**418**	**348[a]**		**307[a]**	
Any medication	51 (75)	58 (84)	228 (81)	350 (84)	256 (74)		232 (76)	
Pre-study Background Inhalers, N (%)								
SABA[b]	34 (50)	40 (58)	150 (54)	235 (56)	196 (56)		153 (50)	
LABA[c]	31 (46)	27 (39)	125 (45)	176 (42)	94 (27)		103 (34)	
LAMA	22 (32)	24 (35)	59 (21)	76 (18)	48 (14)		64 (21)	
Inhaled CS[d]	18 (26)	16 (23)	142 (51)	228 (55)	98 (28)		123 (40)	
SAMA	8 (12)	8 (12)	59 (21)	116 (28)	69 (20)		58 (19)	
Other Pre-study Medication, N (%)								
Mucolytic	2 (3)	2 (3)	5 (2)	12 (3)	4 (1)		7 (2)	
Oxygen[e]	5 (7)	2 (3)	6 (2)	6 (1)	4 (1)		3 (< 1)	
Xanthine	1 (1)	0	25 (9)	32 (8)	8 (2)		10 (3)	
CS[f]	0	0	1 (< 1)	2 (< 1)	NR		NR	

CS = corticosteroid; ITT = intention-to-treat; LABA = long-acting beta2-agonist; LAMA = long-acting muscarinic antagonist; n = number of patients; N = number of patients randomized; NR = not reported; PBO = placebo; SABA = short-acting beta2-agonist; SAMA = short-acting muscarinic antagonist; UMEC = umeclidinium.
[a] Population includes all patients in the ITT population.
[b] Includes a SABA given on its own and in combination with a SAMA.
[c] Includes a LABA given on its own and in combination with an inhaled CS.
[d] Includes an inhaled CS given on its own and in combination with a LABA.
[e] Refers to oxygen taken within 30 days prior to screening.
[f] Systemic, oral, parenteral, or intra-articular CS.
Note: "Pre-study" indicates that medication taken within 30 days prior to screening.
Source: Manufacturer-submitted Clinical Study Reports.[3-6]

3.2.3 Interventions

Medication was delivered via the Ellipta DPI once daily. Placebo and active therapy were identical in appearance and self-administered by the patient. Patients were advised to take their treatment at the same time each morning. Proper use of the inhaler was required for randomization of patients in the exercise endurance studies (DB2114417 and DB2114418). No criterion for proper use of the inhaler was mentioned for the 12-week and 24-week parallel-group studies (AC4115408 and DB2113373). All trials were designed to include a run-in period (lasting five to nine days for study AC4115408, seven to 14 days for DB2113373, and 12 to 21 days for the exercise endurance trials), a double-blind period lasting 12 weeks (AC4115408, DB2114417, DB2114418) or 24 weeks (DB2113373), and a follow-up period of one week.

Only treatment groups that consisted of Health Canada–approved regimens were summarized in this report (Table 11). As such, the results for umeclidinium 125 mcg once daily (above the Health Canada–recommended dose) in the 12-week parallel-group study (AC4115408) and the exercise endurance

studies (DB2114417 and DB2114418) — as well as the results for vilanterol 25 mcg once daily (not approved by Health Canada) in the 24-week parallel-group study (DB2113373) and the exercise endurance studies (DB2114417 and DB2114418) — were excluded from this report. Additionally, please refer to the Anoro Ellipta CDR clinical review report[1] for the efficacy and safety results for umeclidinium/vilanterol 62.5 mcg/25 mcg once daily in the 24-week parallel-group study (DB2113373) and the exercise endurance studies (DB2114417 and DB2114418).

TABLE 11: TREATMENT ARMS INCLUDED, EXCLUDED, OR NOT REPORTED FOR THE INCLUDED STUDIES

	Included		Excluded			Not reported
Study	**Placebo**	**UMEC 62.5 mcg**	**UMEC 125 mcg[a]**	**VI 25 mcg[a]**	**UMEC/VI 125 mcg/25 mcg[a]**	**UMEC/VI 62.5 mcg/25 mcg[b]**
AC4115408	x	x	x	NA	NA	NA
DB2113373	x	x	NA	x	NA	x
DB2114417	x	x	x	x	x	x
DB2114418	x	x	x	x	x	x
DB2116132[c]	NA	x	NA	x	NA	x
DB2116133[c]	NA	x	NA	x	NA	x

NA = not applicable; UMEC = umeclidinium bromide; VI = vilanterol; x = treatment group included in the respective study.
[a] Excluded because dose not approved by Health Canada.
[b] Data presented in CADTH Common Drug Review Anoro Ellipta clinical report.[1]
[c] No study data were extracted due to limitations described in text.
Source: Manufacturer-submitted Clinical Study Reports.[3-6]

Concomitant medication allowed in all studies included inhaled salbutamol as a study-provided relief medication. This medication must not have been used within four hours of spirometry testing. Patients were also allowed to continue using their ICS if they were taking it prior to study entry, provided it was maintained at a consistent dose. If patients switched from LABA/ICS combination therapy to ICS monotherapy, this must have happened at least 48 hours prior to the start of the study. Mucolytics, medications for rhinitis, antibiotics for acute infections, short-term oxygen use, ongoing use of systemic beta-blockers, localized corticosteroid injections, and cautious use of oral muscarinic antagonists were also allowed.

3.2.4 Outcomes

a) Pulmonary function

FEV_1 is the volume of air after a full inspiration that can be forcibly expired in one second. Trough FEV_1 is defined as the mean FEV_1 measured 23 hours and 24 hours after the last scheduled dose administered. It was the primary efficacy end point in studies AC4115408 (at 12 weeks) and DB2113373 (at 24 weeks), as well as the co-primary efficacy end point in studies DB2114417 and DB2114418 (at 12 weeks). The measure was calculated based on the three highest spirometry measures (from a maximum of eight measures) taken at 23 and 24 hours post-dose. Higher scores are indicative of higher functioning and the minimal clinically important difference (MCID) ranges from 0.10 L to 0.14 L, or a 5% to 10% change from baseline (APPENDIX 6).

b) Exercise endurance

Exercise endurance time (EET) is a measure of exercise endurance and was assessed as the length of time that a patient spends performing the endurance shuttle walk test (ESWT). The ESWT is a

standardized, constant-paced field test to assess endurance capacity. Patients are instructed to walk for as long as possible (up to a maximum of 20 minutes). The EET was measured three hours after the last scheduled dose administered (12 weeks), and was the co-primary efficacy end point in the exercise endurance studies (DB2114417 and DB2114418). Higher scores are indicative of better exercise endurance, and the suggested MCID is a within-patient change of 65 or 70 seconds (APPENDIX 6).

c) Lung volumes

Trough inspiratory capacity (IC), FRC, and trough residual volume (RV) were used to measure lung hyperinflation as secondary outcomes in the exercise endurance studies (DB2114417 and DB2114418). Trough IC, FRC, and RV were measured in the same manner as trough FEV_1. Measures were calculated based on the three highest spirometry measures (from a maximum of eight measures) taken at 23 and 24 hours after the last scheduled dose was administered. Higher scores for trough IC, and lower scores on trough FRC and trough RV, are indicative of better functioning. The MCID for these three measures is unknown.

d) Dyspnea

The Transition Dyspnea Index (TDI) is used to measure the severity of dyspnea relative to a patient's baseline state according to functional impairment, magnitude of task, and magnitude of effort. TDI was classified as an "other end point" in studies AC4115408 and DB2113373 (for the regulatory submission to the Food and Drug Administration [FDA]). For the purposes of regulatory submission to the European Medicines Agency (EMA), TDI was considered a key secondary efficacy end point in study DB2113373. The TDI is an interviewer-administered assessment by a trained individual with an advanced knowledge of dyspnea. Each item is graded on a scale of –3 (major deterioration) to +3 (major improvement), for a maximum TDI score range from –9 to +9. Higher scores indicate greater improvements from baseline, and a one-unit change in TDI is considered to be an appropriate MCID (APPENDIX 6).

The Exercise Dyspnea Scale (EDS) is used to assess shortness of breath during exercise, and was measured at two-minute intervals during the ESWT. The EDS is a physician-rated instrument and was assessed in studies DB2114417 and DB2114418. Scores are based on a 10-point modified Borg scale of perceived exertion (i.e., thereafter the 'Borg-scale'), with higher scores indicating worse functioning (i.e., more breathlessness). A one-unit change in the EDS is considered to be an appropriate MCID.[34]

e) Quality of life

The St. George's Respiratory Questionnaire (SGRQ) is a quality-of-life measure that was developed to measure impaired health and perceived well-being for patients with chronic airflow limitation. The SGRQ consists of 50 items (with 76 weighted responses) covering three dimensions: Symptoms (measuring distress due to respiratory symptoms), Activity (measuring the effect of disturbances on mobility and physical activity), and Impacts (measuring the psychosocial impact of the disease). The SGRQ is a patient self-report measure and was assessed as an efficacy outcome in the 12- and 24-week parallel-group studies (AC4115408 and DB2113373). Total SGRQ scores range from 0 to 100, with higher values indicating lower health-related quality of life (HRQoL). A decrease in score indicates an improvement in HRQoL; a decrease of four units in the total score is considered to be an appropriate MCID (APPENDIX 6).

f) Rescue salbutamol use

g) COPD exacerbations

A COPD exacerbation was defined as an acute worsening of COPD symptoms requiring the use of antibiotics, systemic corticosteroids, emergency treatment, or hospitalization (treatment beyond study drug or rescue salbutamol). COPD exacerbations were assessed as a safety end point in the 12-week parallel-group study (AC4115408) and the exercise endurance studies (DB2114417 and DB2114418), and as an efficacy outcome in the 24-week parallel-group study (DB2113373).[3-6] Exacerbations were based on daily patient self-report using a paper diary. The paper diary was reviewed by the study coordinator at each visit.

h) Health care resource utilization

Health care resource utilization was defined as any contact made with a health care provider about the patient's lung condition that was not related to participation in the study. Health care resource utilization was assessed in the 24-week parallel-group study (DB2113373) based on patient self-report data using an eDiary. Patients were asked to record any contact made with a health care provider every evening during the run-in and treatment periods. An entry into the eDiary triggered an email to be sent to the appropriate study site for study personnel for follow-up to obtain detailed information about the contact with the health care provider. Compliance with eDiary completion was monitored on a weekly basis.[4]

i) Patient adherence/satisfaction

In all studies, compliance was assessed by reviewing the dose counter on the Ellipta inhaler. Compliance was assessed at visits 3 to 7 in the 12-week parallel-group study (AC4115408), visits 4 to 8 in the 24-week parallel-group study (DB2113373), and visits 6, 7, 11, and 12 in the exercise endurance studies (DB2114417 and DB2114418).[3-6] The ease of use of the Ellipta inhaler was assessed in the exercise endurance studies (DB2114417 and DB2114418) for the ITT population after six weeks of treatment during treatment period one. Patients were asked to rate the ease of use of the inhaler and how easily they were able to tell how many doses of medication were remaining in the inhaler, both on a five-point scale of 1 (very easy) to 5 (very difficult).[5,6]

j) Harms

Adverse events (AEs) and serious adverse events (SAEs) were assessed in all studies (AC4115408, DB2113373, DB2114417, and DB2114418).[3-6] The detection, documentation, and reporting of AEs and SAEs were the responsibility of the investigator or site staff. All AEs and SAEs were monitored from the second visit (i.e., the first day that the patient received the study drug) until the follow-up visit. All SAEs that were considered to be study-related were monitored from the time the patient consented to participate in the study to the follow-up visit. An AE could include an exacerbation of a condition, emergence of a new condition or signs, symptoms, or clinical sequelae of a suspected interaction or overdose of any treatment (study-related or concomitant). An SAE could include any unexpected medical occurrence that resulted in death, was considered life-threatening, or resulted in disability or hospitalization. Lack of efficacy was considered an AE or SAE if the signs and symptoms resulting from the lack of efficacy met the definition of an AE or SAE. COPD exacerbation was not recorded as an AE unless it was defined as a "serious" AE. Signs and symptoms of COPD that may have been recorded in a patient's paper diary were not considered to be AEs.

3.2.5 Statistical analysis

The 12 week parallel-group study (AC4115408) was powered to test for differences between umeclidinium bromide (125 mcg or 62.5 mcg) and placebo on trough FEV_1 at day 85 (week 12). Sample-size calculations were based on an estimated treatment difference of 130 mL and a standard deviation

(SD) of 210 mL from a previous phase 2b study.[3] These estimates provided 90% power to detect a 130 mL difference between active treatment and placebo groups on trough FEV_1 at day 85 (week 12) (Table 12).

The 24-week parallel-group study (DB2113373) was powered to test for differences between active treatment groups (including umeclidinium 62.5 mcg) and placebo on all primary and secondary end points. Sample-size calculations were based on an estimated treatment difference of 1 unit and a SD of 3.24 units for TDI from a previous study of fluticasone propionate/salmeterol.[4] These estimates provided > 99% power to detect a 100 mL difference between active treatment and placebo groups in the primary outcome trough FEV_1 at day 169 (week 24) (Table 12).

The exercise endurance studies (DB2114417 and DB2114418) were powered to test for differences between umeclidinium 62.5 mcg or 125 mcg/vilanterol 25 mcg and placebo for the co-primary end points EET and trough FEV_1. Sample-size calculations were based on an estimated treatment difference of 70 seconds (SD 160 seconds) for EET and 100 mL (SD 168 mL) for trough FEV_1.[5,6] These estimates provided 94% power to detect differences between umeclidinium 125 mcg or 62.5 mcg/vilanterol 25 mcg and placebo for EET and 92% for trough FEV_1 (Table 12). Based on the sample-size calculations for the primary comparison of interest (umeclidinium/vilanterol 125 mcg/25 mcg or umeclidinium/vilanterol 62.5 mcg/25 mcg versus placebo), there would be 64% power to detect differences between umeclidinium 62.5 mcg and placebo for EET.

TABLE 12: SAMPLE-SIZE CONSIDERATIONS FOR THE INCLUDED STUDIES

	AC4115408	DB2113373[a]	DB2114417[b]		DB2114418[b]	
Primary outcome	Trough FEV_1	Trough FEV_1	EET	Trough FEV_1	EET	Trough FEV_1
Power	90%	> 99%	94%[c]	92%	94%[c]	92%
Significance	5%	5%	5%	5%	5%	5%
Expected difference vs. PBO	130 mL	100 mL	70 s	100 mL	70 s	100 mL
Estimate of residual SD	210 mL	210 mL	114 s[d]	168 mL	114 s[d]	168 mL
Expected withdrawal rate	15%	30%	30%	30%	30%	30%
Planned N (per group)	198 (66)	1,463 (399/299)[e]	312 (12)	312 (12)	312 (12)	312 (12)

EET = exercise endurance time; FEV_1 = forced expiratory volume in one second; N = number of patients; PBO = placebo; s = second; SD = standard deviation; vs. = versus.
[a] Powered for all primary and secondary end points (sample size based on achieving 90% power to detect a one-unit difference between treatments for TDI).
[b] Studies included co-primary end points.
[c] Power calculation was based on the comparison between umeclidinium bromide/vilanterol and placebo. Based on the sample size calculations for the primary analysis, there would be 64% power to detect differences between umeclidinium bromide and placebo.
[d] SD was divided by √2, which assumes a correlation of 0.5 for within-patient outcomes.
[e] 399 patients were to be randomized to active treatment, 299 patients to placebo. Treatment groups weighted higher to collect more safety data.
Source: Manufacturer-submitted Clinical Study Reports.[3-6]

The primary efficacy analysis for the included studies is listed in Table 13. All primary outcomes were assessed using the intention-to-treat (ITT) population and a mixed model for repeated measures analysis. Common covariates across trials included smoking status, centre group, treatment, day/visit, and day/visit by treatment interaction term. The secondary efficacy analyses for the included studies were analyzed in the same manner as the primary efficacy analyses.

TABLE 13: PRIMARY EFFICACY ANALYSIS FOR THE INCLUDED STUDIES

	AC4115408	DB2113373	DB2114417[a]		DB2114418[a]	
Primary outcome	Trough FEV_1	Trough FEV_1	EET[b]	Trough FEV_1	EET[b]	Trough FEV_1
Primary efficacy analysis	MMRM, ITT population					
Covariates						
Smoking status	x	x	x	x	x	x
Centre group	x	x	x	x	x	x
Treatment	x	x	x	x	x	x
Day/visit	x	x	x	x	x	x
Period	NA	NA	x	x	x	x
Baseline FEV_1	x	x	NA	NA	NA	NA
Mean baseline FEV_1	NA	NA	NA	x	NA	x
Period baseline FEV_1	NA	NA	NA	x	NA	x
Mean walking speed	NA	NA	x	NA	x	NA
Period walking speed	NA	NA	x	NA	x	NA
Interaction covariates						
Day/visit × treatment	x	x	x	x	x	x
Day × baseline FEV_1	x	x	NA	NA	NA	NA
Visit × period walking speed	NA	NA	x	NA	x	NA
Visit × mean walking speed	NA	NA	x	NA	x	NA
Visit × period baseline	NA	NA	NA	x	NA	x
Visit × mean baseline	NA	NA	NA	x	NA	x

EET = exercise endurance time; FEV_1 = forced expiratory volume in one second; ITT = intention-to-treat; MMRM = mixed model for repeated measures; NA = not applicable; PBO = placebo; SD = standard deviation; x = covariate included in the analysis.
[a] Studies included co-primary end points.
[b] Three-hour post-dose EET.
Source: Manufacturer-submitted Clinical Study Reports.[3-6]

A step-down, closed testing procedure was used to control for multiple statistical testing in all four included studies (Table 14). The 12-week and 24-week parallel-group studies (AC4115408 and DB2113373) included the comparison of umeclidinium 62.5 mcg versus placebo as part of the statistical testing hierarchy, whereas the exercise endurance studies (DB2114417 and DB2114418) considered this comparison as a supportive analysis and it was not included in the statistical hierarchy.

TABLE 14: CONTROL FOR MULTIPLE STATISTICAL TESTING IN THE INCLUDED STUDIES

Study	Primary end point(s)	Step-down closed testing statistical hierarchy
AC4115408[a]	Trough FEV_1	UMEC 125 mcg versus placebo **UMEC 62.5 mcg versus placebo**
DB2113373[b]	Trough FEV_1	UMEC/VI 62.5 mcg/25 mcg versus placebo **UMEC 62.5 mcg versus placebo** VI 25 mcg versus placebo UMEC/VI 62.5 mcg/25 mcg versus VI 25 mcg UMEC/VI 62.5 mcg/25 mcg versus UMEC 62.5 mcg
DB2114417[c]	Trough FEV_1 & 3-hour post-dose EET	UMEC/VI 125 mcg/25 mcg versus placebo — EET UMEC/VI 125 mcg/25 mcg versus placebo — Trough FEV_1
DB2114418[c]		UMEC/VI 62.5 mcg/25 mcg versus placebo — EET UMEC/VI 62.5 mcg/25 mcg versus placebo — Trough FEV_1

EET = exercise endurance time; FEV_1 = forced expiratory volume in one second; UMEC = umeclidinium; VI = vilanterol.
Bold = comparison of interest in the present review.
[a] No control for multiple statistical testing for secondary or other efficacy end points.
[b] The same testing hierarchy was used for all secondary end points (including TDI, which was identified as the first secondary efficacy end point for submission to the EMA).
[c] No control for multiple statistical testing for outcomes between UMEC 62.5 mcg versus placebo because the comparison was outside of the testing hierarchy and was considered a supportive analysis.
Source: Manufacturer-submitted Clinical Study Reports.[3-6]

All studies performed a sensitivity analyses for missing data using a missing-at-random approach (AC4115408, DB2113373, DB2114417, and DB2114418), copying differences from control approach (AC4115408, DB2113373, DB2114417, and DB2114418), and/or a last mean carried forward approach (AC4115408, DB2113373).

All studies performed sensitivity analyses for a pre-specified list of interaction terms to examine treatment effects across covariates, including smoking status, ICS use, reversibility to salbutamol, and per cent predicted FEV_1. A repeated measures analysis was undertaken that included the covariate and the covariate-by-treatment interaction. If the interaction between the treatment and the covariate was statistically significant at the 10% level across all visits (day 2, week 6, week 12), the treatment effects were assessed separately for each subgroup. In the 12- and 24-week parallel-group studies (AC4115408 and DB2113373), no interaction term met these criteria, so no subgroup analyses were performed. In the exercise endurance studies, further subgroup analyses were performed for trough FEV_1 by reversibility to salbutamol (DB2114417 and DB2114418) and smoking status (DB2114418), and for EET by per cent predicted FEV_1 (DB2114418).

a) Analysis populations

The all-subjects-enrolled (ASE) population included all patients for whom informed consent was received. It included all patients who failed the screening visit and who may have experienced an SAE between obtaining consent and the screening visit.

The ITT population included all randomized subjects who received at least one dose of the study drug.

The per-protocol population included all subjects in the ITT population except those who were identified as full protocol violators. Full protocol violators included subjects who received a study drug other than that to which they were randomized to, or who did not meet the inclusion, exclusion, or randomization criteria that were considered to affect the primary outcome. Partial protocol violators had their data included up to the point that the deviation occurred.

3.3 Patient disposition

The percentage of patients who passed the screening and run-in period from ASE ranged from 49% to 84% across studies (Table 15). Percentages were lower for the exercise endurance studies (49% and 59% for studies DB2114417 and DB2114418 respectively) compared with the 12- and 24-week parallel-group studies (84% and 70% for studies AC4115408 and DB2113373 respectively). Following randomization, the percentage of patients who discontinued from treatment ranged from 5% to 27% across studies, and rates were generally higher in the placebo group (14% to 27% of patients) compared with the umeclidinium 62.5 mcg group (5% to 22% of patients), except for one exercise endurance study (DB2114417), where rates of discontinuation were the same (14% of patients) between the umeclidinium 62.5 mcg group and the placebo group. Lack of efficacy was the most common reason for discontinuation across studies, most often due to COPD exacerbation. Rates of discontinuation due to AEs were higher in the umeclidinium 62.5 mcg groups compared with placebo groups for study AC4115408 (1% versus 0%) and DB2113373 (8% versus 3%), lower in study DB2114417 (4% versus 5%), and the same in study DB2114418 (5% each).

TABLE 15: PATIENT DISPOSITION

	AC4115408		DB2113373		DB2114417		DB2114418	
	PBO	**UMEC 62.5 mcg**	**PBO**	**UMEC 62.5 mcg**	**PBO**	**UMEC 62.5 mcg**	**PBO**	**UMEC 62.5 mcg**
Screened, N	246		2,210		596		634	
Randomized, N (%)	206 (84)		1,536 (70)		349 (59)		308 (49)	
Randomized to treatment groups,[a] N	68	69	280	418	170	49	151	41
Discontinued, n (%)	18 (26)	7 (10)	76 (27)	94 (22)	23 (14)[b]	7 (14)[b]	31 (21)[b]	2 (5)[b]
Adverse event	0	1 (1)	9 (3)	34 (8)	9 (5)	2 (4)	7 (5)	2 (5)
Lack of efficacy	8 (12)	5 (7)	37 (13)	20 (5)	11 (6)	2 (4)	15 (10)	2 (5)
Protocol deviation	0	0	4 (1)	7 (2)	1 (< 1)	0	2 (1)	0
Reached stopping criteria	6 (9)	0	9 (3)	13 (3)	0	1 (2)	0	1 (3)
Lost to follow-up	0	0	1 (< 1)	0	2 (1)	0	1 (< 1)	0
Withdrew consent	4 (6)	1 (1)	16 (6)	20 (5)	0	2 (4)	6 (4)	1 (2)
ITT, n (%)	68 (100)	69 (100)	280 (100)	418 (100)	170 (100)	49 (100)	151 (100)	40 (98)
PP, n (%)	61 (90)	66 (96)	233 (83)	362 (87)	161 (95)	47 (96)	136 (90)	35 (85)
Safety,[c] n (%)	68 (100)	69 (100)	280 (100)	418 (100)	170 (100)	49 (100)	151 (100)	40 (98)

ITT = intention-to-treat; n = number of patients; N = number of patients screened or randomized; PBO = placebo; PP = per-protocol; UMEC = umeclidinium.

[a] Patients also randomized to other study treatment groups.

[b] The percentage of patients who discontinued from the study was based on the sum of occurrences during treatment periods 1 and 2 and the washout period. If discontinuation occurred during the washout period, the event was applied to the count for treatment period 1. The denominator is the number of patients randomized to the treatment group.

[c] Safety results are based on the ITT population; for all AEs, non-fatal SAEs, fatal AEs, and AEs leading to discontinuation of study drug or withdrawal from the study, results are based on the all-subjects-enrolled (ASE) dataset.

Source: Manufacturer-submitted Clinical Study Reports.[3-6]

3.4 Exposure to study treatments

The median exposure to treatment for the 12-week parallel-group study was 83 days for the placebo group and 84 days for the umeclidinium 62.5 mcg group. Patients enrolled in the exercise endurance studies with 12-week treatment periods had a median exposure to treatment of 85 days across treatment groups. For the 24-week parallel-group study, median exposure time was approximately double the exposure time of the 12-week parallel-group studies, with a mean of 167 days in the placebo group and 168 days in the umeclidinium 62.5 mcg group (Table 16). Compliance with treatment was > 98% across all studies and treatment groups (Table 16).

TABLE 16: SUMMARY OF EXPOSURE TO AND COMPLIANCE WITH TREATMENT

	AC4115408		DB2113373		DB2114417		DB2114418	
	PBO	UMEC 62.5 mcg	PBO	UMEC 62.5 mcg	PBO	UMEC 62.5 mcg	PBO	UMEC 62.5 mcg
N	68	69	280	418	170	49	151	40
Exposure								
Median days (range)	83 (1 to 85)	84 (2 to 90)	167 (1 to 177)	168 (1 to 179)	85 (2 to 96)	85 (11 to 91)	85 (1 to 94)	85 (41 to 88)
Compliance								
Mean % (SD)	98.7 (5.5)	98.9 (4.0)	98.3 (8.0)	99.8 (23.3)	99.4 (5.1)	99.8 (6.6)	98.9 (5.1)	98.9 (8.63)

N = number of patients; PBO = placebo; SD = standard deviation; UMEC = umeclidinium.
Source: Manufacturer-submitted Clinical Study Reports.[3-6]

TABLE 17: SUMMARY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE BACKGROUND MEDICATION

	AC4115408		DB2113373		DB2114417		DB2114418	
	PBO	UMEC 62.5 mcg	PBO	UMEC 62.5 mcg	PBO	UMEC 62.5 mcg	PBO	UMEC 62.5 mcg
N	68	69	280	418	170	49	151	40
Any medication, n (%)[a]	25 (37)	18 (26)	140 (50)	230 (55)	52 (31)	11 (22)	68 (45)	17 (43)
On-treatment background inhalers, n (%)								
Inhaled CS	18 (26)	15 (22)	131 (47)	210 (50)	47 (28)	10 (20)	66 (44)	17 (43)
Other on-treatment background medication, n (%)								
Oxygen	5 (7)	2 (3)	7 (3)	6 (1)	3 (2)	0	1 (< 1)	0

COPD = chronic obstructive pulmonary disease; CS = corticosteroid; n = number of patients; N = number of patients randomized; PBO = placebo; UMEC = umeclidinium.
[a] Includes systemic, oral, parenteral, or intra-articular CS.
Note: COPD medication not given for an exacerbation.
Source: Manufacturer-submitted Clinical Study Reports.[3-6]

3.5 Critical appraisal

3.5.1 Internal validity

- There were two short-term studies (DB2116132 and DB2116133) that met the inclusion criteria for the review but were not summarized in full in this report because they had a number of design and methodological limitations. Trough FEV_1 (a key efficacy end point in this review) was measured as a secondary outcome in both studies; however, the studies were not powered to detect a change in this end point. A step-down statistical testing hierarchy was used to control for multiple statistical testing in both studies; however, the only comparison involving Health Canada–approved treatments was umeclidinium 62.5 mcg versus umeclidinium/vilanterol 62.5 mcg/25 mcg, and this treatment comparison was outside of the statistical hierarchy and considered exploratory. The study did not include a treatment group to allow for a comparison between umeclidinium 62.5 mcg and any other long-acting monotherapy or placebo.

- The 12- and 24-week parallel-group studies were powered to test for differences between umeclidinium 62.5 mcg versus placebo for the primary outcome (trough FEV_1) in the 12-week study and primary and secondary outcomes in the 24-week study (including trough FEV_1 and TDI, for which TDI was classified as an "other" end point for the regulatory submission to the FDA).
- The exercise endurance studies (DB2114417 and DB2114418) were not designed to test for differences between umeclidinium 62.5 mcg versus placebo. The randomization strategy was unequal between treatment groups in order to maximize the power to detect differences between umeclidinium/vilanterol and placebo. These studies may have been underpowered to detect differences between umeclidinium 62.5 mcg and placebo across all measured outcomes.
- An a priori statistical testing hierarchy was included for all studies. The 12-week parallel-group study had a hierarchy starting with umeclidinium 125 mcg versus placebo, and the 24-week parallel-group study had a hierarchy starting with umeclidinium/vilanterol 62.5 mcg/25 mcg versus placebo. Statistical significance had to be achieved at the top-level comparisons in order to proceed with statistical testing between umeclidinium 62.5 mcg and placebo. The exercise endurance studies did not include umeclidinium 62.5 mcg versus placebo as part of their statistical testing hierarchy; therefore, there was no control for multiple statistical testing for this comparison, and the analysis was considered exploratory.
- The subgroup analyses that were performed in the exercise endurance studies (DB2114417 and DB2114418) were based on tests for treatment interactions that were not powered, and there was no adjustment for multiple statistical testing.
- In all studies, a randomization code was generated by the sponsor and was communicated to the study sites using an interactive voice response system. Inhalers used in the placebo and active treatment groups were identical in appearance, and patients and physicians in all trials were blinded to patient treatment group. Patients were instructed to take the study medication at the same time each morning.
- In the exercise endurance studies (DB2114417 and DB2114418), correct inhaler use was a criterion for randomization and was reassessed throughout the treatment period. In all studies, treatment adherence was assessed by reviewing the dose counter of the inhaler. If adherence fell below 80%, patients were re-educated on the proper treatment regimen. If poor adherence was routinely found, eligibility for continued participation in the study was discussed by study personnel.
- The proportion of withdrawals in the umeclidinium 62.5 mcg and placebo groups ranged between 5% and 27% across studies. There was a greater percentage discontinuation in the placebo groups in all studies except DB2114417, where 14% of patients discontinued treatment in both groups. The disproportionate rate of withdrawal in the placebo groups compared with the umeclidinium 62.5 mcg group in three of the four included studies may have disrupted the balance of patient characteristics from random allocation, and could potentially threaten the validity of the results.
- More than one multiple imputation method was used to handle the effects of missing data. Missing data imputation approaches included the missing-at-random approach (AC4115408, DB2113373, DB2114417, and DB2114418), copying differences from control (AC4115408, DB2113373, DB2114417, and DB2114418), and last mean carried forward (AC4115408 and DB2113373). The results of all missing data sensitivity analyses supported the results of the main analyses.
- All analyses were based on the set of patients who were randomized and received at least one dose of the study drug. This is not a true ITT population.
- Trough FEV_1 was a primary or co-primary end point in all studies. Trough FEV_1 is a valid outcome measure with an established MCID in patients with COPD, although its correlation with symptoms and its impact on COPD progression are unknown. Further, it is unknown whether the study personnel undertaking the measurement were appropriately trained in spirometry measurement — an important consideration when performing spirometry.[35,36]

- The EET was a co-primary end point in the exercise endurance studies. The validity of this measure is unknown and the reported MCID is variable in the literature (APPENDIX 6).

3.5.2 External validity

- According to the clinical expert involved in this review, the characteristics of the populations in the included studies are generally reflective of patients with moderate to severe COPD. The exercise endurance studies tended to have a greater proportion of females (a finding that the clinical expert stated was also reflective of clinical practice) and a greater percentage of current smokers compared with the 12- and 24-week parallel-group studies.
- Pre-study background inhaler use was low (especially use of LAMA monotherapy) and baseline use of rescue medication was high, a finding that the clinical expert believed is reflective of the suboptimal management of patients with COPD that generally exists in clinical practice.
- Patients with a diagnosis of asthma were excluded from the study population; however, the high proportion of patients experiencing reversibility to salbutamol suggested the possible inclusion of patients with asthma,[37] limiting the generalizability of the results.
- There were a high number of screen failures during the run-in period of the exercise endurance studies (49% and 59%). Patients were excluded during the run-in period if they experienced a COPD exacerbation or did not maintain their regular dose of ICS (if applicable). This randomization criterion may have led to the inclusion of a select group of patients and potentially limited the generalizability of the results.
- All included studies compared umeclidinium 62.5 mcg with one or more of: umeclidinium 125 mcg, umeclidinium/vilanterol 125 mcg/25 mcg, umeclidinium/vilanterol 62.5 mcg/25 mcg, vilanterol 25 mcg, or placebo. There was no direct evidence for the comparative efficacy of umeclidinium 62.5 mcg versus other Health Canada–approved long-acting monotherapy treatments.
- Trough FEV_1 at the end of the treatment period as a primary or co-primary end point is not particularly well correlated to symptoms that are of greatest clinical importance to patients, such as quality of life, especially when measured over shorter time frames.[38]
- Treatment duration in the included studies was 12 or 24 weeks, and length of follow-up was one week. This length of time is sufficient for the assessment of the primary end point trough FEV_1, though it does not provide an indication of the impact on trough FEV_1 in the long-term. This duration also may be insufficient to assess outcomes such as the number of COPD exacerbations and health care resource utilization, as well as notable harms, such as cardiovascular implications and the incidence of pneumonia.[2,37]
- Patients report that they are looking for “drugs that, beyond providing symptomatic or emergency relief, can improve lung function and quality of life, reduce exacerbations, delay disease progression, and, over the long-term, improve survival” (APPENDIX 1). Evidence for the long-term effect (> 24 weeks) of umeclidinium 62.5 mcg on quality of life, COPD exacerbations, disease progression, and survival is not available from the included trials.
- Proper use of an inhaler may be suboptimal in routine clinical practice.[39] Careful monitoring of compliance as it occurs under ideal study conditions may not be reflective of what typically occurs in clinical practice.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported (see Section 2.2, Table 5).

3.6.1 Mortality

No deaths were reported in the 12-week parallel-group study (AC4115408) or the two exercise endurance studies (DB2114417 and DB2114418). In the 24-week parallel-group study (DB2113373), one death occurred in the placebo group (post-treatment due to painful lymph nodes in the neck) and three deaths occurred in the umeclidinium 62.5 mcg group (two post-treatment and one on-treatment) (Table 18 and Table 19). The two post-treatment deaths in the umeclidinium 62.5 mcg group occurred 11 days (due to sudden death) and 18 days (due to cholecystitis and peritonitis) after the last dose of study drug.[4] The on-treatment death reported was due to COPD and acute respiratory failure.[4]

3.6.2 Health care resource utilization

Health care resource utilization was documented in the 24-week parallel-group study (DB2113373). A higher percentage of patients in the umeclidinium 62.5 mcg group had reported a visit to the emergency room or urgent care centre compared with the placebo group (1.9% versus 1.1%). The percentage of patients who were admitted to hospital during the study period was also higher for the umeclidinium 62.5 mcg group compared with the placebo group (1.4% versus 0.4%) (Table 18).

3.6.3 Chronic obstructive pulmonary disease exacerbations

The percentage of patients experiencing a COPD exacerbation was higher in the placebo group than in the umeclidinium 62.5 mcg group in all four studies (Table 18 and Table 19). In the 12 week parallel-group study (AC4115408), 10% of patients in the placebo group and 7% of patients in the umeclidinium 62.5 mcg group experienced an exacerbation. Thirteen per cent of patients in the placebo group and 8% of patients in the umeclidinium 62.5 mcg group experienced a COPD exacerbation in the 24-week parallel-group study (DB2113373). There was a greater differential between placebo and umeclidinium 62.5 mcg groups in the percentage of patients experiencing an exacerbation in one exercise endurance study (DB2114418, 10.6% versus 0%) compared with the other (DB2114417, 6.5% versus 2.0%).

There were a higher percentage of patients experiencing severe consequences from COPD exacerbations for the umeclidinium 62.5 mcg group compared with the placebo group in the 24-week parallel-group study (DB2113373), with a higher percentage of patients visiting the emergency room (4.5% versus 2.9%) and/or being hospitalized (3.3% versus 1.1%) due to an exacerbation. No patient in either group of the 12-week parallel-group study (AC4115408) or in the umeclidinium 62.5 mcg group of the exercise endurance studies (DB2114417 and DB2114418) went to the emergency room or were hospitalized due to a COPD exacerbation. One per cent of patients visited the emergency room, and one per cent experienced a hospitalization in the placebo groups of the exercise endurance studies (DB2114417 and DB2114418) due to a COPD exacerbation.

3.6.4 Pulmonary function tests

a) Trough FEV_1

The least squares (LS) mean change from baseline in trough FEV_1 was the primary outcome in the 12- and 24-week parallel-group studies (AC4115408 and DB2113373) and the co-primary end point in the exercise endurance studies (DB2114417 and DB2114418). The LS mean trough FEV_1 at end of treatment ranged from 1.24 L to 1.49 L across studies, and the adjusted mean change from baseline to end of treatment ranged from –0.007 L to 0.004 L for the placebo groups and 0.05 L to 0.12 L for the umeclidinium 62.5 mcg groups (Table 18, Table 19).

The generally accepted MCID for FEV_1 is between 0.10 L and 0.14 L, or a change of 5% to 10% from baseline (APPENDIX 6). Compared with placebo, there was a statistically and clinically significant greater mean change from baseline to end of treatment for the primary end point, trough FEV_1, for the

umeclidinium 62.5 mcg group compared with placebo in the 12-week parallel-group study (AC4115408, umeclidinium 62.5 mcg versus placebo LS mean change 0.13 L; 95% CI, 0.05 to 0.20) and the 24-week parallel-group study (DB2113373, umeclidinium 62.5 mcg versus placebo: LS mean change 0.12 L [95% CI, 0.08 to 0.16]).

There was a statistically significantly greater mean change from baseline to week 12 for trough FEV_1 in the umeclidinium 62.5 mcg group compared with the placebo group in the exercise endurance studies (DB2114417, umeclidinium 62.5 mcg versus placebo: LS mean change 0.09 L [95% CI, 0.03 to 0.14; *P* = 0.003]; DB2114418, umeclidinium 62.5 mcg versus placebo: LS mean change 0.14 L [95% CI, 0.09 to 0.20]). The mean change from baseline to 12 weeks for umeclidinium 62.5 mcg versus placebo is unlikely to be clinically significant (LS mean change: < 0.1 L) in one exercise endurance study (DB2114417); clinical significance was reached for mean change from baseline to 12 weeks for umeclidinium 62.5 mcg versus placebo in the other exercise endurance study, DB2114418 (LS mean change: > 0.1 L).

Subgroup analysis

Reversibility to salbutamol: Patients in the umeclidinium 62.5 mcg group who were reversible to salbutamol experienced a statistically significant greater mean change from baseline in trough FEV_1 versus patients in the placebo group in both exercise endurance studies (LS mean change versus placebo in DB2114417: 0.15 L [95% CI, 0.06 to 0.24]; in DB2114418: 0.12 L [95% CI, 0.03 to 0.21]). In one exercise endurance study (DB2114418), patients in the umeclidinium 62.5 mcg group who were not reversible to salbutamol experienced a statistically significantly greater mean change from baseline in trough FEV_1 versus patients in the placebo group (LS mean change versus placebo: 0.16 L [95% CI, 0.08 to 0.24]). There were no statistically significant differences between treatment groups for patients who were not reversible to salbutamol in the other exercise endurance study (DB2114417), in which LS mean change versus placebo was 0.05 L [95% CI, –0.02 to 0.12]) (APPENDIX 4, Table 21).

Smoking status: Patients in the umeclidinium 62.5 mcg group had a statistically significantly greater mean change from baseline in trough FEV_1 versus patients in the placebo group regardless of smoking status (in DB2114418, current smoker LS mean change from baseline versus placebo was 0.11 L [95% CI, 0.04 to 0.19]; for former smokers, the LS mean change from baseline versus placebo was 0.19 L [95% CI, 0.10 to 0.28]) (APPENDIX 4, Table 22).

3.6.5 Symptoms

The key symptom assessed in the included studies was dyspnea as measured by TDI focal score.

a) Dyspnea

TDI focal score was classified as an “other” efficacy end point in the 12-week parallel-group study (AC4115408) and the 24 week parallel-group study (DB2113373) for the regulatory submission to the FDA. For the purposes of regulatory submission to the EMA, TDI was considered a key secondary efficacy end point in the 24-week parallel-group study (DB2113373). The within-group adjusted mean TDI score for the umeclidinium 62.5 mcg group was 0.7 units at 12 weeks in study AC4115408, and 2.2 units at 24 weeks in study DB2113373. The adjusted mean for umeclidinium 62.5 mcg versus placebo was not statistically significant in the 12-week study (LS mean versus placebo 1.0 [95% CI, 0.0 to 2.0; *P* = 0.05]), but was statistically significant in the 24-week study (LS mean versus placebo: 1.0 [95% CI, 0.5 to 1.5; *P* < 0.001]). The change versus placebo was equal to the MCID of one unit in both studies.

3.6.6 Health-related quality of life

The SGRQ was used to assess quality of life in the 12- and 24-week parallel-group studies (AC4115408 and DB2113373). Higher scores are indicative of greater impairment; a change from baseline of four units is considered a clinically meaningful change (APPENDIX 6). At baseline, the mean SGRQ total score was 46 for both the placebo group and the umeclidinium 62.5 mcg group in the 12-week parallel-group study; it was 49 and 51 for the umeclidinium 62.5 mcg group and placebo group, respectively, in the 24-week parallel-group study. In the 12-week study, there was an adjusted mean improvement in scores from baseline to the end of treatment in the umeclidinium 62.5 group of –3.1 units and a statistically and clinically significant mean change from baseline to end of treatment versus placebo (LS mean change versus placebo: –7.9 [95% CI, –12.2 to –3.6; $P < 0.001$]). In the 24-week parallel-group study, there was a clinically significant within-group change from baseline to end of treatment (–7.3) for the umeclidinium 62.5 mcg group, and a statistically and clinically significant mean change from baseline to end of treatment for the umeclidinium 62.5 mcg group versus placebo (LS mean change versus placebo: –4.7 [95% CI, –7.1 to –2.3; $P < 0.001$]) (Table 18).

3.6.7 Function and disability

No measures of function and disability were assessed in the included studies.

3.6.8 Exercise tolerance

a) Three-hour post-dose exercise endurance time

Three-hour post-dose EET was a co-primary end point in the exercise endurance studies (DB2114417 and DB2114418). Higher scores indicate greater functioning and a change from baseline of 65 seconds or 70 seconds is indicative of a clinically meaningful change (APPENDIX 6). At baseline, mean scores were numerically lower in the umeclidinium 62.5 mcg group compared with the placebo group in both studies. There was a numerically greater adjusted mean change from baseline to end of treatment (12 weeks) in the placebo group of one exercise endurance study (DB2114417) (36.7 seconds) compared with the placebo group in the other exercise endurance study (DB2114418) (0.1 seconds). Similarly, the umeclidinium 62.5 mcg group of study DB2114417 had a numerically greater adjusted mean change from baseline to end of treatment (12 weeks) (63.2 seconds) than the umeclidinium 62.5 mcg group in study DB2114418 (25.1 seconds). There were no statistically or clinically significant differences between the umeclidinium 62.5 mcg groups and placebo groups in three-hour post-dose EET at week 12 in either study (LS mean change versus placebo in DB2114417: 26.5 [95% CI, –25.9 to 78.9; $P = 0.32$]; in DB2114418: 25.0 [95% CI, –41.0 to 91.0; $P = 0.17$]) (Table 19).

Subgroup analysis

Chronic obstructive pulmonary disease severity: Patients in the umeclidinium 62.5 mcg group who were classified as GOLD Stage III and IV experienced a statistically significantly greater mean change from baseline in three-hour post-dose EET versus patients in the placebo group in one exercise endurance study (LS mean change versus placebo in study DB2114418: 130.2 seconds [95% CI, 24.9 to 235.4]). There were no statistically significant differences in three-hour post-dose EET between treatment groups for patients classified as GOLD stage I and II in study DB2114418 (LS mean change versus placebo: –62.4 seconds [95% CI, –145.4 to 20.6]) (APPENDIX 4, Table 23).

Exercise dyspnea scale

Dyspnea during exercise was measured in the exercise endurance studies (DB2114417 and DB2114418) using the modified Borg scale. Higher scores are indicative of more severe dyspnea, and a change of 1.0 unit is considered clinically meaningful.[34] The adjusted mean level of dyspnea at 12 weeks was 3.7 units for the placebo group and 3.5 units in the umeclidinium 62.5 mcg group in study DB2114417, and 3.3

units for the placebo group and 3.0 units for the umeclidinium 62.5 mcg group in study DB2114418. The adjusted mean change from baseline to 12 weeks was numerically greater in the umeclidinium 62.5 mcg group compared with the placebo group in both studies, but did not reach statistical or clinical significance in either study (LS mean change versus placebo in DB2114417: –0.2 [95% CI, –0.6 to 0.3; *P* = 0.5]; in DB2114418: –0.32 [95% CI, –0.78 to 0.13; *P* = 0.17]) (Table 19).

b) Lung volumes

Trough inspiratory capacity

Trough IC was assessed in the exercise endurance studies (DB2114417 and DB2114418). Higher scores are indicative of better functioning. There was a numerically greater increase in trough IC at 12 weeks in the umeclidinium 62.5 mcg group compared with the placebo group in both studies. The adjusted mean change from baseline versus placebo did not reach statistical significance in either study (LS mean change versus placebo in study DB2114417: 0.03 L [95% CI, –0.07 to 0.13; *P* = 0.59]; in study DB2114418: 0.10 L [95% CI, –0.01 to 0.20; *P* = 0.06]) (Table 19).

Trough forced residual capacity

Trough FRC was assessed in the exercise endurance studies (DB2114417 and DB2114418). Lower scores are indicative of better functioning. There was a numerically greater decrease in trough FRC at 12 weeks in the umeclidinium 62.5 mcg group compared with the placebo group in both studies. There was a statistically significant mean change from baseline versus placebo in one exercise endurance study (LS mean change from baseline versus placebo in DB2114417: –0.28 L [95% CI, –0.48 to –0.09; *P* = 0.005]) but not in the other (LS mean change from baseline versus placebo in DB2114418: –0.12 L [95% CI, –0.29 to 0.06; *P* = 0.19]) (Table 19).

Trough respiratory volume

Trough RV was assessed in the exercise endurance studies (DB2114417 and DB2114418). Lower scores are indicative of better functioning. There was a numerically greater decrease in trough RV at 12 weeks in the umeclidinium 62.5 mcg group compared with the placebo group in both studies. The adjusted mean change from baseline versus placebo reached statistical significance in both studies (LS mean change versus placebo in study DB2114417: –0.38 L [95 % CI, –0.58 to –0.17; *P* < 0.001]; in DB2114418: –0.22 L [95% CI, –0.40 to –0.03; *P* = 0.02]) (Table 19).

TABLE 18: KEY EFFICACY OUTCOMES: 12- AND 24-WEEK PARALLEL-GROUP STUDIES (AC4115408 AND DB2113373)

Outcome	AC4115408 (12 Weeks)		DB2113373 (24 Weeks)	
	PBO	UMEC 62.5 mcg	PBO	UMEC 62.5 mcg
N	68	69	280	418
Mortality, n (%)				
All-cause	0	0	1[a]	2 (0.5)[a]
COPD-related	0	0	0	1 (0.2)[b]
Health Care Resource Utilization,[c] n (%)				
Emergency room or urgent care	NA	NA	3 (1.1)	8 (1.9)
Admitted to hospital	NA	NA	1 (0.4)	6 (1.4)
COPD Exacerbation, n (%)[c]				
Number of subjects experiencing an exacerbation	7 (10.3)	5 (7.2)	35 (12.5)	33 (7.9)

Outcome	AC4115408 (12 Weeks)		DB2113373 (24 Weeks)	
	PBO	UMEC 62.5 mcg	PBO	UMEC 62.5 mcg
Emergency room	0	0	8 (2.9)	19 (4.5)
Hospitalized	0	0	3 (1.1)	14 (3.3)
Trough FEV_1 (L)				
LS mean (SE)	1.24 (0.03)	1.36 (0.03)	1.24 (0.02)	1.35 (0.01)
LS mean change (SE)	–0.007 (0.03)	0.12 (0.03)	0.004 (0.02)	0.12 (0.01)
LS mean change versus PBO (95% CI)[d]	NA	0.13 (0.05 to 0.20)	NA	0.12 (0.08 to 0.16)
P value	NA	< 0.001	NA	< 0.001
Dyspnea (TDI Focal Score)				
LS mean (SE)	–0.3 (0.38)	0.7 (0.34)	1.2 (0.20)	2.2 (0.16)
LS mean versus PBO (95% CI)[e]	NA	1.0 (0.0 to 2.0)	NA	1.0 (0.5 to 1.5)
P value	NA	0.05[f]	NA	< 0.001
Quality of Life (SGRQ Total Score)				
Baseline mean (SD)	46.4 (17.9)	45.9 (16.4)	51.3 (18.1)	48.8 (18.2)
LS mean (SE)	50.3 (1.6)	42.4 (1.5)	46.6 (1.0)	41.9 (0.8)
LS mean change (SE)	4.8 (1.6)	–3.1 (1.5)	–2.6 (1.0)	–7.3 (0.8)
LS mean change versus PBO (95% CI)[g]	NA	–7.9 (–12.2 to –3.6)	NA	–4.7 (–7.1 to –2.3)
P value	NA	< 0.001[g]	NA	< 0.001[g]
Use of Rescue Medication, No. of Puffs Per Day (Week 1 To EOT)				
Baseline mean (SD)	3.6 (4.7)	3.0 (3.2)	5.9 (6.3)	5.5 (5.7)
LS mean (SE)	2.9 (0.24)	2.2 (0.22)	4.1 (0.20)	3.8 (0.16)
LS mean change (SE)	–0.0 (0.24)	–0.7 (0.22)	–1.4 (0.20)	–1.7 (0.16)
LS mean change versus PBO (95% CI)[h]	NA	–0.7 (–1.3 to –0.1)	NA	–0.3 (–0.8 to 0.2)
P value	NA	0.03[g]	NA	0.28[g]

CI = confidence interval; COPD = chronic obstructive pulmonary disease; EOT = end of treatment; FEV_1 = forced expiratory volume in one second; LS = least squares; n = number of patients; N = number of patients randomized; NA = not applicable; No. = number; PBO = placebo; SD = standard deviation; SE = standard error; SGRQ = St. George's Respiratory Questionnaire; TDI = Treatment Dyspnea Index; UMEC = umeclidinium bromide.

[a] Deaths occurred post-treatment (one in the placebo group related to painful lymph nodes in the neck, and two in the umeclidinium 62.5 mcg group: one due to sudden death and one due to cholecystitis and peritonitis).

[b] One death occurred on-treatment (due to COPD and acute respiratory failure).

[c] Percentage is based on the N for each treatment group as the denominator.

[d] Repeated measures analysis controlling for: treatment, baseline (FEV_1 pre-dose), smoking status, centre group, day, day × baseline, day × treatment.

[e] Repeated measures analysis controlling for: treatment, baseline (BDI focal score), smoking status, centre group, day, day × baseline, day × treatment.

[f] No control for multiple statistical testing (outside of the testing hierarchy).

[g] Repeated measures analysis controlling for: treatment, baseline (SGRQ pre-dose day 1), smoking status, centre group, day, day × baseline, day × treatment.

[h] Analysis of covariance controlling for: treatment, baseline (mean number of puffs pre-treatment) smoking status and centre group.

Source: Manufacturer-submitted Clinical Study Reports;[3,4] manufacturer provided additional information.[33]

TABLE 19: KEY EFFICACY OUTCOMES — EXERCISE ENDURANCE STUDIES (DB2114417 AND DB2114418)

Outcome	DB2114417 (12 Weeks)		DB2114418 (12 Weeks)	
	PBO	UMEC 62.5 mcg	PBO	UMEC 62.5 mcg
N	170	49	151	40
Mortality, n (%)				
All-cause	0	0	0	0
COPD-related	0	0	0	0[a]
COPD Exacerbation, n (%)[b]				
Number of subjects	11 (6.5)	1 (2.0)	16 (10.6)	0
Visited emergency room	2 (1.2)	0	1 (0.7)	0
Hospitalized	2 (1.2)	0	2 (1.3)	0
3-Hour Post-dose EET (seconds)				
Baseline mean (SD)	316.1 (171.8)	280.5 (152.7)	339.7 (193.0)	318.0 (167.0)
Week 12 mean (SD)	347.6 (245.8)	330.2 (205.2)	351.5 (212.6)	329.9 (232.3)
LS mean change (SE)	36.7 (13.2)	63.2 (23.9)	0.1 (16.7)	25.1 (30.2)
LS mean change versus PBO (95% CI)[e]	NA	26.5 (–25.9 to 78.9)	NA	25.0 (–41.0 to 91.0)
P value	NA	0.32[d]	NA	0.46[d]
Trough FEV_1 (L)				
LS mean (SE)	1.40 (0.01)	1.49 (0.03)	1.28 (0.02)	1.42 (0.03)
LS mean change (SE)	–0.03 (0.02)	0.05 (0.03)	–0.04 (0.02)	0.10 (0.03)
LS mean change versus PBO (95% CI)[c]	NA	0.09 (0.03 to 0.14)	NA	0.14 (0.09 to 0.20)
P value	NA	0.003[d]	NA	< 0.001[d]
Trough IC (L)				
Baseline mean (SD)	2.26 (0.61)	2.28 (0.49)	2.14 (0.7)	2.14 (0.6)
LS mean (SE)	2.26 (0.03)	2.28 (0.05)	2.15 (0.03)	2.24 (0.05)
LS mean change (SE)	–0.002 (0.03)	0.03 (0.05)	–0.02 (0.03)	0.08 (0.05)
LS mean change versus PBO (95% CI)[c]	NA	0.03 (–0.07 to 0.13)	NA	0.10 (–0.01 to 0.20)
P value	NA	0.59[d]	NA	0.06[d]
Trough FRC (L)				
Baseline mean (SD)	4.76 (1.26)	4.85 (1.28)	4.87 (1.37)	4.75 (1.05)
LS mean (SE)	4.80 (0.05)	4.47 (0.09)	4.72 (0.05)	4.60 (0.08)
LS mean change (SE)	0.02 (0.05)	–0.26 (0.09)	–0.08 (0.05)	–0.20 (0.08)
LS mean change versus PBO (95% CI)[c]	NA	–0.28 (–0.48 to –0.09)	NA	–0.12 (–0.29 to 0.06)
P value	NA	0.005[d]	NA	0.19[d]
Trough RV (L)				
Baseline mean (SD)	4.05 (1.17)	4.10 (1.26)	4.01 (1.27)	3.82 (1.01)
LS mean (SE)	4.05 (0.05)	3.68 (0.09)	3.91 (0.05)	3.69 (0.08)
LS mean change (SE)	0.04 (0.05)	–0.34 (0.09)	–0.05 (0.05)	–0.27 (0.08)
LS mean change versus PBO (95% CI)[c]	NA	–0.38 (–0.58 to –0.17)	NA	–0.22 (–0.40 to –0.03)
P value	NA	< 0.001[d]	NA	0.02[d]

Outcome	DB2114417 (12 Weeks)		DB2114418 (12 Weeks)	
	PBO	UMEC 62.5 mcg	PBO	UMEC 62.5 mcg
EDS (at iso-time)				
LS mean (SE)	3.7 (0.1)	3.5 (0.2)	3.3 (0.11)	3.0 (0.21)
LS mean change (SE)	–0.3 (0.1)	–0.5 (0.2)	–0.01 (0.11)	–0.33 (0.21)
LS mean change versus PBO (95% CI)[f]	NA	–0.2 (–0.6 to 0.3)	NA	–0.32 (–0.78 to 0.13)
P value	NA	0.5[d]	NA	0.17[d]
Use of Rescue Medication, No. of Puffs Per Day (Week 1 To 12)				
Baseline mean (SD)	2.7 (3.0)	2.8 (2.9)	3.6 (3.8)	2.6 (2.1)
LS mean (SE)	2.4 (0.11)	2.2 (0.19)	3.0 (0.14)	2.3 (0.25)
LS mean change (SE)	–0.4 (0.11)	–0.6 (0.19)	–0.3 (0.14)	–1.0 (0.25)
LS mean change versus PBO (95% CI)[g]	NA	–0.2 (–0.6 to 0.1)	NA	–0.7 (–1.3 to –0.2)
P value	NA	0.21[d]	NA	0.006[d]

CI = confidence interval; COPD = chronic obstructive pulmonary disease; EDS = Exercise Dyspnea Scale; EET = exercise endurance time; FEV_1 = forced expiratory volume in one second; FRC = functional residual capacity; IC = inspiratory capacity; iso-time = the time point that the individual patient's baseline walking time was taken; LS = least squares; N = number of patients randomized; n = number of patients; NA = not applicable; no. = number; PBO = placebo; RV = residual volume; SD = standard deviation; SE = standard error; UMEC = umeclidinium bromide.

[a] One on-treatment death occurred (due to malignant lung neoplasm and metastases to the central nervous system) for a patient receiving UMEC 62.5 mcg during treatment period 1 and UMEC/VI 62.5/25 mcg during treatment period 2. The death occurred during treatment with UMEC/VI 62.5/25 mcg.

[b] Percentage is based on the N for each treatment group as the denominator.

[c] Repeated measures analysis controlling for: period baseline, mean baseline, period, treatment, visit, smoking status, centre group, visit × period, visit × mean baseline, and visit × treatment.

[d] No control for multiple statistical testing; comparisons between PBO and UMEC 62.5 mcg were considered supportive analysis.

[e] Repeated measures analysis controlling for: period walking speed, mean walking speed, period, treatment, visit, smoking status, centre group, visit × period walking speed, visit × mean walking speed, and visit × treatment.

[f] Repeated measures analysis controlling for: period baseline, mean baseline, period, treatment, visit, smoking status, centre group, visit × period baseline, visit × mean baseline, and visit × treatment.

[g] Analysis of covariance controlling for: treatment, period baseline, mean baseline, period, smoking status, and centre group.

Source: Manufacturer-submitted Clinical Study Reports;[5,6] manufacturer provided additional information.[33]

3.6.9 Other efficacy outcomes

a) Use of rescue medication

All studies assessed changes in the use of rescue medication from baseline to the end of treatment. Baseline use of rescue medication was highest in the 24-week parallel-group study (DB2113373), with a mean of 5.5 puffs per day in the umeclidinium 62.5 mcg group and 5.9 puffs per day in the placebo group. In the 12-week parallel-group study (AC4115408) and the exercise endurance studies (DB2114417 and DB2114418), baseline use of rescue medication ranged between a mean of 2.6 and 3.6 puffs per day and was generally similar between groups, except in study DB2114418, where patients in the umeclidinium 62.5 mcg group had a mean of 2.6 puffs per day and patients in the placebo group had a mean of 3.6 puffs per day. There were reductions in the mean number of puffs per day used by patients across all umeclidinium 62.5 mcg groups and placebo groups of the included trials, with numerically greater reductions in the umeclidinium 62.5 mcg groups. The statistical significance of changes in rescue medication use was variable between trials. There was a statistically significant greater decrease in the use of rescue medication from baseline to end of treatment for the umeclidinium 62.5 mcg group compared with the placebo group in the 12-week parallel-group study and in one exercise endurance study (LS mean change versus placebo in study AC4115408: –0.7 [95% CI, –1.3

to –0.1; *P* = 0.03]; in study DB2114418: –0.7 [95% CI, –1.3 to –0.2; *P* = 0.28]), but not for the 24-week parallel-group study or the other exercise endurance study (LS mean change versus placebo in study DB2113373: –0.3 [95% CI, –0.8 to 0.2; *P* = 0.28]; in study DB2114417: –0.2 [95% CI, –0.6 to 0.1; *P* = 0.21]) (Table 18, Table 19).

b) Patient adherence and satisfaction

Based on the ITT population in one exercise endurance study (DB2114417), 98% of patients indicated that the Ellipta device was either easy (29%) or very easy (69%) to use at six weeks (treatment period one).[5] Likewise, at six weeks (treatment period one) in the other exercise endurance study (DB2114418), 99% of patients indicated that the Ellipta device was either easy (20%) or very easy (79%) to use.[6]

c) Days of missed work/xchool

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

3.7 Harms

Only those harms identified in the review protocol are reported (see Section 2.2, Table 5).

3.7.1 Adverse events

The proportion of patients experiencing an AE varied across trials, ranging from 12% in the umeclidinium 62.5 mcg group of study DB2114417 to 52% in the umeclidinium 62.5 mcg group of study DB2113373 (Table 20). The 24-week parallel-group study (DB2113373) was the longest duration of the four included studies, and had the highest proportion of patients experiencing AEs. The percentage of patients experiencing AEs was numerically higher in the placebo group compared with the umeclidinium 62.5 mcg group in the exercise endurance studies (in DB2114417: placebo 27% versus umeclidinium 62.5 mcg 12%; in DB2114418, placebo 39% versus umeclidinium 62.5 mcg 30%). The percentage of patients experiencing an AE in the 12-week parallel-group study (AC4115408) was generally similar between placebo and umeclidinium 62.5 mcg groups. The most common AEs across all trials were headache and nasopharyngitis.

3.7.2 Serious adverse events

The proportion of patients experiencing SAEs ranged between 0% and 6% across treatment groups of the included studies (Table 20). The 24-week parallel-group study (DB2113373) was the longest of the four included studies, and had the highest proportion of patients experiencing SAEs. The percentage of patients experiencing an SAE was higher for the umeclidinium 62.5 mcg group compared with placebo in study DB2113373 (6% versus 3%), and lower in the umeclidinium 62.5 mcg group compared with placebo for study DB2114417 (0% versus 4%). The percentage of patients experiencing an SAE was similar between the placebo and umeclidinium 62.5 mcg groups in studies AC4115408 and DB2114418.

3.7.3 Withdrawals due to adverse events

The proportion of patients who withdrew due to an AE ranged from 0% to 8% across treatment groups of the included studies (Table 20). The 24-week parallel-group study (DB2113373) was the longest of the four included studies and had the highest proportion of patients who withdrew due to an AE (8% in the umeclidinium 62.5 mcg group versus 3% in the placebo group). WDAEs were one or two percentage points higher in the placebo groups compared with the umeclidinium 62.5 mcg groups in the exercise endurance studies (DB2114417: 5% versus 4%; DB2114418: 5% versus 3%) and in the umeclidinium 62.5 mcg group compared with the placebo group in the 12-week parallel-group study (AC4115408 1% versus 0%).

3.7.4 Notable harms

The percentage of patients experiencing a cardiovascular-related event ranged from 1% to 10% across treatment groups of the included studies (Table 20). Percentages were highest in the 24-week parallel-group study (9% in the placebo group and 10% in the umeclidinium 62.5 mcg group), and were generally similar between the umeclidinium 62.5 mcg and placebo groups across all trials. Anticholinergic effects were generally rare across treatment groups and studies, ranging from 0% to 4% of patients. The percentage of patients experiencing anticholinergic effects was highest in the 24-week parallel-group study (4% in the umeclidinium 62.5 mcg group and 3% in the placebo group). No anticholinergic effects were reported for patients in the umeclidinium group of the exercise endurance studies or the 12-week parallel-group study. Cases of pneumonia were similarly rare across study groups and trials, ranging from 0% to 2% of patients affected.

TABLE 20: HARMS

Outcome	AC4115408		DB2113373		DB2114417		DB2114418	
	PBO	UMEC 62.5 mcg	PBO	UMEC 62.5 mcg	PBO	UMEC 62.5 mcg	PBO	UMEC 62.5 mcg
N	68	69	280	418	170	49	151	40
AEs, n (%)[a]	24 (35)	27 (39)	130 (46)	216 (52)	46 (27)	6 (12)	59 (39)	12 (30)
Headache	7 (10)	5 (7)	26 (9)	32 (8)	7 (4)	0	8 (5)	1 (3)
Nasopharyngitis	7 (10)	8 (12)	16 (6)	29 (7)	10 (6)	1 (2)	10 (7)	4 (10)
Back pain	4 (6)	2 (3)	7 (3)	8 (2)	4 (2)	0	5 (3)	0
Cough	1(1)	0	7 (3)	16 (4)	2 (1)	0	3 (2)	0
URTI	0	2 (3)	14 (5)	21 (5)	0	0	1 (< 1)	0
Oropharyngeal pain	1 (1)	0	4 (1)	6 (1)	2 (1)	0	3 (2)	0
Bursitis	0	2 (3)	1 (< 1)	0	NR	NR	0	0
COPD	0	0	3 (1)	12 (3)	1 (< 1)	0	1 (< 1)	0
Arthralgia	1 (1)	0	3 (1)	12 (3)	0	1 (2)	2 (1)	1 (3)
SAEs, n (%)	1 (1)	1 (1)	9 (3)	27 (6)	6 (4)	0	4 (3)	1 (3)
WDAEs, n (%)	0	1 (1)	9 (3)	34 (8)	9 (5)	2 (4)	8 (5)	1 (3)
Notable harms, n (%)								
Cardiovascular	1 (1)	2 (3)	26 (9)	41 (10)	6 (4)	1 (2)	2 (1)	1 (3)
Arrhythmia	1 (1)	2 (3)	12 (4)	20 (5)	1 (< 1)	0	0	0
Ischemia	0	0	3 (1)	7 (2)	1 (< 1)	0	2 (1)	0
Hypertension	0	0	6 (2)	12 (3)	3 (2)	1 (2)	0	0
Cardiac failure	NR	NR	5 (2)	7 (2)	0	0	0	1 (3)
Anticholinergic	3 (4)	0	8 (3)	18 (4)	2 (1)	0	6 (4)	0
Dizziness	0	0	4 (1)	3 (< 1)	2 (1)	0	1 (< 1)	0
Dry mouth	0	0	1 (< 1)	3 (< 1)	0	0	1 (< 1)	0
Dysphagia	1 (1)	0	1 (< 1)	0	0	0	1 (< 1)	0
Pyrexia	1 (1)	0	1 (< 1)	3 (< 1)	0	0	1 (< 1)	0
Blurred vision	1 (1)[b]	0	1 (< 1)	1 (< 1)	0	0	2 (1)	0
Pneumonia	0	0	2 (< 1)	6 (1)	1 (< 1)	1 (2)	2 (1)	0

AE = adverse event; n = number of patients; NR = not reported; PBO = placebo; SAE = serious adverse event; UMEC = umeclidinium bromide; URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse event.

[a] Reported by ≥ 3% of subjects.

[b] One patient experienced a visual hallucination.

Source: Manufacturer-submitted Clinical Study Reports.[3-6]

4. DISCUSSION

4.1 Summary of available evidence

Six manufacturer-sponsored trials were included in the review. Two of the six studies (DB2116132 and DB2116133) were short-term (14-day), three-way randomized crossover trials. Due to a number of design and methodological limitations (i.e., primary outcome selection, statistical testing hierarchy, and the prioritization of treatment comparisons), it was difficult to make inferences on the findings from these studies in the context of this review and so presentation of data from these studies was limited to Sections 3.1 and 3.2.1 of this report.

The four remaining studies included two parallel-group studies (AC4115408 [12 weeks] and DB2113373 [24 weeks]) and two two-way randomized crossover trials with 12-week intervention periods (DB2114417 and DB2114418). The two parallel-group studies were designed to assess umeclidinium 62.5 mcg versus placebo for the primary outcome (trough FEV_1) at the end of treatment according to a statistical hierarchy, preceded by umeclidinium 125 mcg versus placebo in the 12-week parallel-group study (AC4115408) and umeclidinium/vilanterol 62.5 mcg/25 mcg versus placebo in the 24-week parallel-group study (DB2113373). Secondary and other outcomes included TDI, SGRQ, rescue salbutamol use, and health care resource utilization (DB2113373).

Both of the two-way randomized crossover trials (DB2114417 and DB2114418) were exercise endurance studies that were primarily designed to assess the combination umeclidinium/vilanterol versus placebo for the co-primary end points, trough FEV_1 and three-hour post-dose EET. Secondary and other outcomes included lung hyperinflation volumes (IC, FRC, and RV), EDS, and rescue salbutamol use. The studies were not designed specifically to compare umeclidinium 62.5 mcg versus placebo, and were considered an exploratory comparison.

A key limitation of the included studies was the short duration (12 weeks and 24 weeks) of the trials, which, although sufficient for the assessment of the primary end point trough FEV_1, may be insufficient to assess outcomes such as the number of COPD exacerbations and health care resource utilization, as well as notable harms such as cardiovascular implications. Other limitations included the study design and power calculations for the exercise endurance studies; these were not optimized for the comparison of interest in this review (umeclidinium 62.5 mcg versus placebo), and there was no direct evidence to compare umeclidinium 62.5 mcg with other long-acting monotherapy treatments. Consequently, there were no long-term efficacy and safety data (> 24 weeks); there were limitations on the interpretability of longer-term outcomes that are meaningful to patients (such as frequency of exacerbations, disease progression, and survival), and there was no comparative safety or efficacy data.

4.2 Interpretation of results

4.2.1 Efficacy

One on-treatment death was reported among the four included studies due to COPD and acute respiratory failure in the umeclidinium 62.5 mcg group of the 24-week parallel-group trial (DB2113373) compared with no on-treatment deaths in the placebo group. One study assessed health care resource utilization (DB2113373) and reported a low percentage of patients with health care resource use. There was a small percentage difference (of 0.8% and 1%) between the placebo and umeclidinium 62.5 mcg groups in the proportion of patients with emergency department visits and hospital admissions, respectively. Patient group input identified that patients are looking for drugs that can improve survival over the long term, rather than providing only symptomatic or emergency relief (APPENDIX 1); however,

the meaningfulness of the mortality and health care resource utilization data was limited given the short duration of trials.

All studies assessed the frequency of COPD exacerbations experienced by patients. Frequency of COPD exacerbations is an important efficacy outcome in interventional studies, particularly exacerbations that lead to emergency room visits or hospitalizations. More frequent exacerbations can accelerate a decline in lung function.[35] The concern regarding exacerbations was also highlighted in patient group input, indicating that exacerbations are also associated with greater anxiety, worsening quality of life, social withdrawal, more exacerbations, and increased risk of hospitalization and mortality (APPENDIX 1). The 24-week parallel-group trial (DB2113373) showed the highest proportion of patients experiencing an exacerbation and the greatest percentage of patients visiting the emergency room or being admitted to hospital as a result of the exacerbation compared with the 12 week trials (AC4115408, DB2114417, and DB2114418).

Fewer than 2% of patients in the 12-week studies visited the emergency room or were admitted to hospital due to a COPD exacerbation. These results suggest that the duration of the study may have been insufficient for measuring this outcome. Due to possible reporting biases with self-reported outcomes, it is possible that the number of exacerbations was under-reported.[40] Although this under-reporting may be balanced among treatment groups, this bias is still a concern given that our interpretation is based on numerical, not statistical, comparisons between groups.[41,42] Results for COPD exacerbations are also influenced by the exacerbation history of the patients enrolled. COPD exacerbation history was measured in the included studies as the number of COPD exacerbations that occurred within 12 months prior to the screening visit. Given the infrequency of COPD exacerbations for patients in the included studies, and the short durations of studies, it is unlikely that a difference between in-treatment effects for COPD exacerbations would be seen. Finally, an EMA guidance suggests a one-year study period for evaluating COPD exacerbations, so the 12- and 24-week durations of the included trials are not likely to provide enough time to draw meaningful conclusions between treatments.[2]

FEV_1 is the most widely used measure to assess the efficacy of drug treatments in current COPD clinical trials.[37] Trough FEV_1 was the primary or co-primary end point in all four included studies, and there was a statistically significant increase in trough FEV_1 from baseline to end of treatment across each of the four studies versus placebo. The results exceeded the clinically significant threshold of a 0.10 L change in all studies except for one exercise endurance study (DB2114417). Trough FEV_1 offers consistent and reproducible results, and is a validated surrogate end point of disease status,[37] although its correlation with symptoms and impact on COPD progression are unknown (APPENDIX 6APPENDIX 6: VALIDITY OF OUTCOME MEASURES).

The EMA suggested that a co-primary end point such as an evaluation of exercise capacity be used when lung function is selected as a primary end point.[2] If improvement can be shown in an exercise endurance test, this is likely to be better correlated with quality of life and a patients' real-life activity. EET was the co-primary end point in the exercise endurance studies (DB2114417 and DB2114418) and the comparison between umeclidinium 62.5 mcg and placebo was considered an exploratory analysis (i.e., prioritized outside of the statistical hierarchy). There were no statistically or clinically significant improvements in EET in either study; however, it is possible that the studies were underpowered to detect change in EET for the comparison between umeclidinium 62.5 mcg and placebo. A priori sample-size calculations indicated that with the anticipated sample size, there would be 64% power to detect

differences between groups. Regardless of the power concerns, no clinically important difference was found between umeclidinium 62.5 mcg and placebo on the EET.

Lung volumes are of particular interest for patients with COPD and — similar to EET — are believed to have a stronger correlation with activity limitations compared with trough FEV_1.[43,44] In the exercise endurance studies, lung volume results as measured by trough IC, FRC, and RV suggest a trend for improvement from baseline to the end of treatment with the use of umeclidinium 62.5 mcg. Results were statistically significant for trough FRC in study DB2114417 and trough RV for studies DB2114417 and DB2114418, but were not statistically significant for trough IC in either study. As suggested by the clinical expert involved in the review, the interpretation of these results was limited by the short duration of trials and the high percentage of current smokers. It is possible that the length of the trials and the high percentage of smokers (61% and 63%) may have lessened patients' overall treatment responsiveness. The numerical and statistical difference in results between the two studies also makes interpretation of the results difficult and any overall conclusions less definitive.

Dyspnea was the main symptom of COPD assessed in the 12- and 24-week parallel-group studies (AC4115408 and DB2113373) using the TDI, and in the exercise endurance studies (DB2114417 and DB2114418) using the EDS (modified Borg scale). There were statistically significant improvements in dyspnea in the 24-week parallel-group study. The efficacy results for measures of dyspnea were not overwhelmingly strong. TDI scores were clinically significant, just having met the clinically important difference threshold of 1.0 unit for the 12- and 24-week parallel-group studies. There were no statistically or clinically significant changes in EDS scores in the exercise endurance studies and a surprisingly high numerical drop in dyspnea scores in the placebo group of one exercise endurance study (placebo LS mean change: –0.3 units [0.1]) (DB2114417).

HRQoL was assessed using the SGRQ in the 12- and 24-week parallel-group studies (AC4115408 and DB2113373). There was a statistically and clinically significant improvement in SGRQ total scores for the umeclidinium 62.5 mcg group versus placebo in both studies. LS mean change in SGRQ total score for the umeclidinium 62.5 mcg group compared with placebo was numerically lower in the 24-week parallel-group study (AC4115408) compared with the 12-week parallel-group study (DB2113378). Input from the patient group stated that early retirement often occurs due to limitations in patients' ability to perform occupational activities. Outcomes that measure the impact of COPD on patients' occupational activities were not assessed in the included studies.

Other efficacy end points included the use of rescue medication and patient adherence/satisfaction. Baseline rescue medication use in the 24-week parallel-group study (DB2113378) was high, indicating suboptimal control of COPD (six puffs of rescue medication per day). No statistically significant differences between umeclidinium 62.5 mcg and placebo were found in the 24-week parallel-group study. According to the clinical expert involved in the review, the exercise endurance studies had more reasonable baseline use of rescue medication (two to four puffs per day), but there was a large difference in baseline use between treatment groups in one study (DB2114418: 2.6 puffs per day among those taking umeclidinium 62.5 mcg versus 3.6 puffs per day for the placebo group). More than 98% of patients in both exercise endurance studies indicated that the Ellipta device was easy or very easy to use — an important element of patient adherence,[39] and a constant challenge for patients with COPD (APPENDIX 1).

Patient group input suggested that diminishing effectiveness associated with the long-term use of some medications should be addressed (APPENDIX 1). None of the included studies addressed the effectiveness of umeclidinium 62.5 mcg over the long term.

There was no direct evidence available to assess the efficacy of umeclidinium 62.5 mcg versus other long-acting monotherapy treatments in the included studies. Given this limitation, the manufacturer submitted an indirect treatment comparison (ITC) to compare the efficacy and safety of umeclidinium 62.5 mcg to tiotropium 18 mcg, aclidinium 400 mcg, and glycopyrronium 50 mcg for the treatment of COPD. Comparative efficacy was based on a measure of trough FEV_1, SGRQ total score, TDI focal score and rescue medication use at weeks 12 and 24. There were 24 studies included in the review and the quantity of evidence was largest for the comparison between tiotropium and placebo (n = 14). No head-to-head trials were identified, so it was not possible to evaluate the level of consistency between direct and indirect evidence. The results of the ITC suggested that there is no statistically or clinically significant difference in outcomes between umeclidinium 62.5 mcg and tiotropium 18 mcg, aclidinium 400 mcg, or glycopyrronium 50 mcg. Other key efficacy outcomes such as health care resource use, COPD exacerbations, and exercise tolerance were not evaluated in the ITC and there was a substantial degree of clinical heterogeneity identified among the included studies (APPENDIX 5).

4.2.2 Harms

The percentage of patients who experienced AEs was variable across studies and treatment groups. The most common AEs were headache, nasopharyngitis, back pain, cough, and upper respiratory tract infections (URTIs). SAEs and WDAEs were generally low, with no consistently observable differences between umeclidinium 62.5 mcg and placebo treatment groups.

The product monograph cautions against the use of umeclidinium 62.5 mcg in patients with narrow-angle glaucoma, urinary retention, and severe cardiovascular disorders.[21] LAMAs are a class of bronchodilators for which notable harms include anticholinergic and cardiovascular effects,[45] and these precautions are noted for other LAMAs.[22-25] Umeclidinium 62.5 mcg was generally well tolerated by patients across studies and treatment groups with respect to notable harms. These findings are consistent with what has been found for other LAMAs.[8,45,46] The percentage of patients with pneumonia was low (≤ 2%). Given that the manifestation of some AEs, such as cardiovascular effects and pneumonia, may take time to materialize, the duration of the included studies makes it difficult to draw convincing conclusions about these outcomes.

Patient groups expressed concern about dry mouth and voice hoarseness from current bronchodilators, as well as AEs that manifest themselves following the management of acute exacerbation with prednisone or antibiotics (e.g., stomach upset, general swelling, symptoms of osteoporosis, and eye problems). No cases of voice hoarseness were reported, and fewer than 1% of patients across treatment groups in the included studies experienced dry mouth.

It is possible that the high percentage of patients discontinuing treatment and the disproportionately higher number of patients discontinuing in the placebo group compared with the umeclidinium 62.5 mcg group of most studies (except DB2114417, in which the percentage of patients who discontinued was 14% in both groups) may have biased the harms data that emerged from the included studies. The high rate of discontinuations may have resulted in an underestimation of the rate of anticholinergic effects experienced by the umeclidinium 62.5 mcg groups. The higher rate of anticholinergic effects in the placebo group compared with the umeclidinium group is surprising and counter-intuitive given the AEs commonly associated with LAMAs.

There is no direct or indirect evidence available to assess the safety of umeclidinium 62.5 mcg versus other long-acting monotherapy treatments in the included studies. The manufacturer-submitted ITC did not contain any safety outcomes, so the comparative safety of umeclidinium 62.5 mcg is unknown.

5. CONCLUSIONS

Six manufacturer-sponsored trials met the inclusion criteria for this review. Two double-blind, randomized parallel-group trials and two double-blind, randomized crossover studies were summarized in this review. Overall, the strength of the evidence was limited for several key efficacy outcomes of interest — including mortality, health care resource utilization, and COPD exacerbations — due to the short study durations. There were statistically significant gains in lung function as measured by the primary efficacy end point of the included studies — trough FEV_1 — after 12 weeks and 24 weeks of treatment with umeclidinium 62.5 mcg, and clinically significant improvements in all but one study. The exercise endurance studies evaluated outcomes of particular clinical importance to patients; however, given the short duration of trials and the variability in results between seemingly similarly conducted trials, the interpretation of results was difficult, and overall conclusions were less definitive. In light of these limitations, there were improvements in lung volume and air trapping measures (trough FRC and RV) among patients taking umeclidinium 62.5 mcg, but no statistically significant improvements in EET. SAEs and WDAEs were generally low, with no consistently observable differences between umeclidinium 62.5 mcg and placebo treatment groups across trials. Umeclidinium 62.5 mcg was generally well tolerated by patients with respect to cardiovascular effects, anticholinergic effects, and cases of pneumonia; however, no long-term data were available. Indirect evidence suggested no difference in the comparative efficacy of umeclidinium 62.5 mcg versus other LAMAs. There was no direct or indirect evidence available to assess the comparative safety of umeclidinium 62.5 mcg versus other long-acting monotherapy treatments.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH Common Drug Review (CDR) staff based on 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

One patient group provided input for this submission.

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 as well as 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 Canada, Novartis Pharmaceuticals, and Nycomed/Takeda Canada; educational grants from ProResp Inc.; and a general grant from GlaxoSmithKline (GSK) Canada. COPD Canada declared no conflict of interest in the preparation of this submission.

2. Condition and current therapy-related information

The information included in this section is based primarily on personal experiences of the members of COPD Canada, as well as on published scientific literature related to the disease. Information provided by patients was obtained in group pulmonary rehabilitation settings or from direct, one-on-one consultations with the members. COPD Canada also had conversations with non-member COPD patients.

COPD is a disease associated with considerable burdens on patients, their families, the health care system, and society as a whole. Patients' everyday lives are affected, including their ability to breathe, talk, sleep, work, and socialize. With worsening disease, patients with COPD will become progressively less physically active and consequently have reduced social contacts. This often creates a downward, vicious cycle. Early retirement occurs due to limitations in patients' occupational activities. As the disease progresses, patients need to adapt their lifestyles in order to cope with their condition. These adaptations can include walking very slowly, avoiding restaurants 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. Furthermore, patients often feel socially isolated, suffer social stigma, and experience depression. Exacerbations are a concern for patients, as they are associated with both short- and long-term consequences on overall health, such as a decline in lung function, greater anxiety, worsening quality of life, social withdrawal, additional exacerbations, and increased risk of hospitalization and mortality.

Caregivers, who are often the children and spouses of those with COPD, and their families, are also heavily affected by the disease. Consequences of caregiving include limited time for managing their own health; feelings of isolation, anxiety, stress, depression, and fatigue; unending days; and increased need for social support. Adult children caring for their parents are often torn between caring for their parent and caring for 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 symptom control and prevention or minimization of the frequency and duration of exacerbations. The main non-drug interventions include pulmonary rehabilitation exercises, breathing lessons, and the use of supplemental oxygen. Surgical interventions include lung transplantation and lung reduction surgery — options that are only available to a small group of patients who qualify for the procedures.

Typical maintenance therapies include Spiriva once per day with Advair twice per day. While this treatment provides some relief, side effects include dry mouth (Spiriva) and voice hoarseness (Advair). Exacerbations are often managed with prednisone and antibiotics. While prednisone works quickly, it is associated with numerous side effects, such as stomach upset, general swelling, symptoms of osteoporosis, and eye problems. Rescue medications are used for symptom control, but they do not improve long-term lung function.

Patients are looking for drugs that, beyond providing symptomatic or emergency relief, can improve lung function and quality of life, reduce exacerbations, delay disease progression, and, over the long term, improve survival. Diminishing of the effectiveness in the long-term use of some medications should be addressed as well. In addition, therapies that offer a convenient treatment option for COPD patients who require long-term maintenance therapy are desirable.

3. Related information about the drug being reviewed

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

Patients with COPD anticipate that Incruse 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 medications. Incorrect use of inhalers is a constant challenge in COPD. The long-acting, once-daily treatment of Incruse Ellipta delivered via a pre-loaded, easy-to-use Ellipta inhaler should provide relief and help with compliance. From the perspective of COPD Canada, any new product that encourages compliance by being an easy-to-use, once-daily morning treatment that decelerates or limits the need for rescue inhalers benefits the health care system by reducing overall costs to the patient and the health care system while improving the patient's quality of life.

4. Additional information

Accessing the 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 coverage in Ontario).

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:	March 27, 2015
Alerts:	Bi-weekly search updates until project completion
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded
SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY		
#	**Searches**	**Results**
1	(Incruse* or umeclidinium* or GSK573719 or GSK 573719 or GSK573719A or GSK 573719A).ti,ot,ab,sh,rn,hw,nm. or (869185-19-3 or 869113-09-7).rn,nm.	197
2	1 use pmez	52
3	*umeclidinium/ or (Incruse* or umeclidinium* or GSK573719 or GSK 573719 or GSK573719A or GSK 573719A).ti,ab.	120
4	3 use oemezd	69
5	4 not conference abstract.pt.	58
6	2 or 5	110
7	remove duplicates from 6	67

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:	March 27, 2015
Keywords:	Incruse Ellipta, umeclidinium, COPD, emphysema, chronic bronchitis
Limits:	No date or language limits used

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

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

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Donohue JF, Anzueto A, Brooks J, Mehta R, Kalberg C, Crater G. A randomized, double-blind dose-ranging study of the novel LAMA GSK573719 in patients with COPD. Respir Med. 2012 Jul;106(7):970-9.	Inappropriate study design (phase 2)
Church A, Beerahee M, Brooks J, Mehta R, Shah P. Dose response of umeclidinium administered once or twice daily in patients with COPD: a randomised crossover study. BMC Pulm Med. 2014;14:2.	Inappropriate study design (phase 2)
Trivedi R, Richard N, Mehta R, Church A. Erratum: Umeclidinium in patients with COPD: a randomised, placebo-controlled study. Eur Respir J. 2014 Aug;44(2):555.	Erratum for Trivedi et al. 2014

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 21: SUBGROUP ANALYSIS FOR TROUGH FEV_1 ACCORDING TO REVERSIBILITY TO SALBUTAMOL (STUDIES DB2114417 AND DB2114418)

Outcome	Reversible		Non-reversible	
	PBO	UMEC 62.5 mcg	PBO	UMEC 62.5 mcg
	Study DB2114417			
Trough FEV_1 (L)				
N; n at week 12	66; 57	19; 16	104; 91	30; 27
LS mean (SE)	1.40 (0.02)	1.55 (0.04)	1.41 (0.02)	1.46 (0.03)
LS mean change (SE)	–0.04 (0.02)	0.11 (0.04)	–0.03 (0.02)	0.02 (0.03)
LS mean change versus PBO (95% CI)[a]	NA	0.15 (0.06 to 0.24)	NA	0.05 (–0.02 to 0.12)
P value	NA	0.002	NA	0.186
	Study DB2114418			
Trough FEV_1 (L)				
N; n at week 12	58; 46	18; 17	89; 71	20; 19
LS mean (SE)	1.29 (0.02)	1.40 (0.04)	1.27 (0.02)	1.44 (0.04)
LS mean change (SE)	–0.04 (0.02)	0.08 (0.04)	–0.05 (0.02)	0.12 (0.04)
LS mean change versus PBO (95% CI)[a]	NA	0.12 (0.03 to 0.21)	NA	0.16 (0.08 to 0.24)
P value	NA	0.01	NA	< 0.001

CI = confidence interval; FEV_1 = forced expiratory volume in one second; LS = least squares; N = number of patients randomized; n = number of patients; NA = not applicable; PBO = placebo; SE = standard error; UMEC = umeclidinium bromide.
[a] Repeated measures analysis controlling for: period baseline, mean baseline, period, treatment, visit, smoking status, centre group, reversibility to salbutamol subgroup, visit × period, visit × mean baseline, visit × treatment, reversibility to salbutamol subgroup × treatment, reversibility to salbutamol subgroup × treatment × visit.
Note: Interaction term significant at $P < 0.1$ (DB2114417: $P = 0.006$; DB2114418: $P = 0.097$).
Source: Manufacturer-submitted Clinical Study Reports.[5,6]

TABLE 22: SUBGROUP ANALYSIS FOR TROUGH FEV_1 ACCORDING TO SMOKING STATUS (STUDY DB2114418)

Outcome	Current Smoker		Former Smoker	
	PBO	UMEC 62.5 mcg	PBO	UMEC 62.5 mcg
Trough FEV_1 (L)				
	Study DB2114418			
N; n at week 12	89; 72	24; 23	60; 47	16; 15
LS mean (SE)	1.27 (0.02)	1.39 (0.03)	1.28 (0.02)	1.47 (0.04)
LS mean change (SE)	–0.05 (0.02)	0.07 (0.03)	–0.04 (0.02)	0.15 (0.04)
LS mean change versus PBO (95% CI)[a]	NA	0.11 (0.04 to 0.19)	NA	0.19 (0.10 to 0.28)
P value	NA	0.003	NA	< 0.001

CI = confidence interval; FEV_1 = forced expiratory volume in one second; L = litres; LS = least squares; N = number of patients randomized; n = number of patients; NA = not applicable; PBO = placebo; SE = standard error; UMEC = umeclidinium bromide.
[b] Repeated measures analysis controlling for: period baseline, mean baseline, period, treatment, visit, smoking status, centre group, visit × period, visit × mean baseline, visit × treatment, smoking status × treatment, smoking status × treatment × visit.
Note: Interaction term significant at $P < 0.1$ (DB2114418: $P = 0$ .008).
Source: Manufacturer-submitted Clinical Study Report.[6]

TABLE 23: SUBGROUP ANALYSIS FOR THREE-HOUR POST-DOSE EXERCISE ENDURANCE TIME ACCORDING TO GLOBAL INITIATIVE FOR OBSTRUCTIVE LUNG DISEASE STAGE (STUDY DB2114418)

Outcome	GOLD Stage I and II		GOLD Stage III and IV	
	PBO	UMEC 62.5 mcg	PBO	UMEC 62.5 mcg
Three-hour post-dose EET (s)				
	Study DB2114418			
N; n at week 12	76; 58	24; 23	69; 57	14; 13
LS mean change (SE)	29.2 (22.6)	–33.1 (37.0)	–30.0 (23.2)	100.1 (49.1)
LS mean change versus PBO (95% CI)[a]	NA	–62.4 (–145.4 to 20.6)	NA	130.2 (24.9 to 235.4)
P value	NA	0.14	NA	0.02

CI = confidence interval; EET = exercise endurance time; GOLD = Global Initiative for Obstructive Lung Disease; LS = least squares; N = number of patients randomized; n = number of patients; NA = not applicable; PBO = placebo; SE = standard error; UMEC = umeclidinium bromide.
[a] Repeated measures analysis controlling for: period walking speed, mean walking speed, period, treatment, visit, smoking status, centre group, visit × period walking speed, visit × mean walking speed, visit × treatment, per cent predicted FEV_1 subgroup × treatment, per cent predicted FEV_1 × treatment × visit.
Note: Interaction term significant at $P < 0.1$ (DB2114418: $P = 0.044$).
Source: Manufacturer-submitted Clinical Study Report.[6]

APPENDIX 5: CRITICAL APPRAISAL OF MANUFACTURER-SUBMITTED INDIRECT TREATMENT COMPARISON BETWEEN INCRUSE ELLIPTA AND OTHER DRUG THERAPIES

1. Objectives

The manufacturer submitted an indirect treatment comparison (ITC) between umeclidinium and other long-acting muscarinic antagonist (LAMA) monotherapy in the treatment of chronic obstructive pulmonary disease (COPD).[47] The objective of this review is to provide a summary and critical appraisal of this ITC.

2. Summary of indirect comparison analysis

Rationale

Long-acting bronchodilators for COPD, LAMAs in particular, are recommended in the current practice guidelines. Because no head-to-head randomized trials comparing umeclidinium with other LAMA monotherapies were identified through a systematic literature search, an ITC was performed by the manufacturer to estimate the comparative efficacy of umeclidinium versus the appropriate comparators.

2.1 Methods

2.1.1 Eligibility criteria

The inclusion criteria for the ITC consisted of the following:

- Population: adult patients with COPD (defined by Global Initiative for Obstructive Lung Disease [GOLD] guidelines) who were eligible for COPD maintenance therapy
- Intervention and comparators: randomized controlled trials (RCTs) comparing umeclidinium 62.5 mcg, tiotropium 18 mcg, aclidinium bromide 400 mcg, or glycopyrronium 50 mcg with each other or with placebo
- Outcomes: lung function (trough forced expiratory volume in one second [FEV_1]), health-related quality of life (HRQoL) (based on St. George's Respiratory Questionnaire [SGRQ] score), COPD symptoms (Transition Dyspnea Index [TDI] focal score), or rescue medication use at week 12 and week 24
- Study design: RCTs with parallel groups and study duration of at least 12 weeks.

In order to identify relevant studies for this ITC, a systematic search of the literature was performed to identify RCTs that met the eligibility criteria stated above. The literature was searched in multiple databases on October 18, 2013, using predefined search strategies. There were no time restrictions in the search. The search was restricted to English language only. Study selection was performed by one reviewer on the full-text reports and verified by a second reviewer. Data extraction was performed by one reviewer and reviewed by a second reviewer. It is unclear whether the risk of bias of the included RCTs was assessed.

2.1.2 Interventions and comparators

The interventions of interest in the ITC were LAMAs: umeclidinium 62.5 mcg once daily, tiotropium 18 mcg once daily, aclidinium bromide 400 mcg twice daily, and glycopyrronium 50 mcg once daily. Umeclidinium 125 mcg once daily was also compared with the other LAMAs in the ITC. This is not a Health Canada–approved dosage; therefore, findings from these comparisons were not included in this report.

2.1.3 Outcomes

Studies reporting one of the following outcomes were included: change in trough FEV_1; SGRQ total score; TDI focal score; and rescue medication use at week 12 and week 24.

2.1.4 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 (placebo in this ITC) using traditional pairwise random-effect meta-analysis. Random-effects models (instead of fixed-effects models) were used to synthesize individual study results for the purpose of accounting for potential unexplained imbalances between the studies,[48] even though most of the statistical testing for heterogeneity did not identify statistical heterogeneity across the included studies. All outcome measures were continuous variables. The point estimates and their 95% confidence intervals were reported in this step. The second step was to indirectly estimate the relative effectiveness of the investigational drug (umeclidinium) to the comparators. Results of the ITC were presented as mean difference in change from baseline with 95% confidence intervals and corresponding probability value.

The statistical heterogeneity was assessed by means of the Cochran Q, chi-square test, and the I^2 statistic with 95% confidence interval, while the clinical heterogeneity was assessed by means of study design; inclusion criteria related to FEV_1, FEV_1/forced residual capacity (FVC), exacerbations, and smoking status; background treatment with inhaled corticosteroids (ICS) and/or long-acting beta2-agonists (LABA); randomization; blinding; open-label groups; and crossover design. Patient's baseline characteristics were also considered: exacerbation history, proportion of patients per COPD severity level, COPD duration, mean FEV_1% predicted, proportion of current smokers, mean pack-years, percentage of male patients, and mean age. Random-effect meta-regression was not performed due to the low number of included studies.

Besides the base-case analysis, two scenario analyses were performed in the indirect comparison of umeclidinium 62.5 mcg and tiotropium 18 mcg. In the first scenario analysis, results of the studies comparing umeclidinium 62.5 mcg with placebo were replaced with integrated summary of efficacy data from four GlaxoSmithKline (GSK) trials: AC4115408, DB2113361, DB2113373, and DB2113374. The second scenario analysis evaluated the effect of adding more reference treatments than placebo, such as umeclidinium 125 mcg, umeclidinium/vilanterol 62.5/25 mcg, and vilanterol 25 mcg. No scenario analyses were performed for the comparison of umeclidinium 62.5 mcg versus aclidinium bromide 400 mcg or versus glycopyrronium 50 mcg. This review focuses on the Health Canada–approved drugs and dosages. Therefore, only results of base-case analyses are reported.

The checklist developed by the Institute for Quality and Efficiency in Health Care (IQWiG) was adopted for a risk of bias assessment.[48] It was unknown whether the potential publication bias was examined in this ITC.

2.2 Results

2.2.1 Study and patient characteristics

A total of 24 RCTs were included in this ITC:

- 2 were umeclidinium versus placebo (DB2113373 and AC4115408)
- 14 were tiotropium versus placebo (Chan 2007, TIPHON, UPLIFT, Niewoehner 2005, Brusasco 2003, Donohue 2002, Casaburi 2002, Donohue 2010, Verkindre 2006, Casaburi 2000, Covelli 2005, Garcia 2007, Moita 2008, and Vogelmeier 2008)

- 2 were tiotropium versus combination therapy of umeclidinium/vilanterol (DB2113374 and DB2113360)
- 3 were aclidinium bromide versus placebo (ACCORD 1, ACCORD 2, and ATTAIN)
- 1 was glycopyrronium versus placebo (GLOW 1)
- 2 were tiotropium versus glycopyrronium versus placebo (GLOW 2 and SHINE)

Placebo was the common comparator with the investigating drugs. These 24 trials were all double-blind, multi-centre parallel trials, but two included tiotropium as open-label group. The study duration ranged from 12 weeks to four years.

The inclusion criteria in these trials varied in terms of post-bronchodilator FEV_1 in most of the tiotropium trials; however, the FEV_1 requirement was similar in the umeclidinium trials (≤ 70%), the aclidinium bromide trials (within 30% to 80%), and the glycopyrronium trials (within 30% to 80%). $FEV_1/FVC \leq 0.70$ was required in all trials in addition to the FEV_1 requirements. ICS was allowed as background treatment in 22 trials, while two tiotropium versus placebo trials did not report whether ICS was permitted. Salbutamol or albuterol were allowed as rescue medication in 13 trials, but not allowed in two tiotropium versus placebo trials. It was unclear whether salbutamol or albuterol were allowed as rescue medication in nine trials.

The number of enrolled patients in these 11 trials ranged from 100 to 5,993. The mean age across all trials was similar, ranging from 60 to 68 years. Significant heterogeneity, however, existed in the baseline patient characteristics across all trials: the majority of patients were male (the proportion of male ranged from 49% to 99%); the proportion of current smokers ranged from 24% to 58%; the proportion of patients with severe or very severe COPD varied from 31% to 62%; ICS use varied from 22% to 71%; and the time since COPD diagnosis ranged from 5.9 years to 12.2 years. The baseline FEV_1% predicted ranged from 0.35 to 0.57. The percentage of reversibility post-salbutamol and the proportion of patients with exacerbations in the year prior to randomization were not reported in this report.

The differences in trial and patient characteristics of the included RCTs in the ITC are presented in Table 24.

TABLE 24: TRIAL CHARACTERISTICS AND PATIENT CHARACTERISTICS OF THE INCLUDED RCTS IN THE ITC

Trials	Post-Bronchodilator FEV_1 Requirement	Rescue Salbutamol or Albuterol Use	% of Males	% of Current Smokers	% of Severe or Very Severe COPD	% of ICS Use	Baseline FEV_1 % Predicted
TIO vs. PBO (14 trials)	≤ 50%: 1 trial ≤ 60%: 4 trials ≤ 65%: 4 trials ≤ 70%: 3 trials 20% to 70%: 1 trial 30% to 80%: 1 trial	Allowed: 4 trials Not allowed: 2 trials Unclear: 8 trials	49 to 99	24 to 40	32 to 62	35 to 71	0.35 to 0.56
TIO vs. GLYCO vs. PBO (2 trials)	30% to 80%: 2 trials	Allowed: 2 trials	64 to 77	39 to 46	32 to 38	51 to 59	0.55 to 0.56
TIO vs. combination therapy (2 trials)	≤ 70%: 2 trials	Allowed: 2 trials	65 to 71	42 to 58	50 to 61	40 to 53	0.46 to 0.48
GLYCO vs. PBO (1 trial)	30% to 80%: 1 trial	Unclear: 1 trial	81 to 83	33 to 34	38 to 40	51 to 55	0.54 to 0.55
AC vs. PBO (3 trials)	30% to 80%: 3 trials	Allowed: 3 trials	50 to 69	42 to 56	31 to 54	39 to 58	0.50 to 0.57
UMEC vs. PBO (2 trials)	≤ 70%: 2 trials	Allowed: 2 trials	61 to 74	47 to 57	51 to 63	22 to 52	0.45 to 0.48

AC = aclidinium; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second; GLYCO = glycopyrronium; ICS = inhaled corticosteroid; PBO = placebo; TIO = tiotropium; UMEC = umeclidinium; vs. = versus.

2.2.2 Results of the indirect treatment comparison

a) Change from baseline for trough forced expiratory volume in one second

Week 12

Umeclidinium versus tiotropium

Results were based on two umeclidinium trials; nine tiotropium trials were pooled separately in two meta-analyses. The umeclidinium trials were generally statistically homogeneous (umeclidinium trials: $I^2 = 0$, $P = 0.777$), while statistically significant heterogeneity was observed across the tiotropium trials due to the varied patient characteristics at baseline and to the study design ($I^2 = 54.9\%$, $P = 0.023$). Results from a random-effects ITC indicated that there was no statistically significant difference between umeclidinium and tiotropium for trough FEV_1 (difference: 0.02 L [95% CI, –0.02 to 0.06; $P = 0.341$]).

Umeclidinium versus aclidinium bromide

Results from five studies were used (two umeclidinium trials and three aclidinium bromide trials). Tests for heterogeneity were not statistically significant across trials (umeclidinium trials: $I^2 = 0$, $P = 0.777$; aclidinium bromide trials: $I^2 = 33.8\%$, $P = 0.221$). The difference between umeclidinium and aclidinium bromide was not statistically significant for this outcome (difference: 0.04 L [95% CI, –0.01 to 0.08; $P = 0.108$]).

Umeclidinium versus glycopyrronium

Results from five studies (two umeclidinium trials and three glycopyrronium trials) were pooled separately in two different meta-analyses. The trials synthesized by each meta-analysis were statistically homogeneous (umeclidinium trials: $I^2 = 0$; $P = 0.777$; glycopyrronium trials: $I^2 = 0$; $P = 0.595$). ITC results indicated that there was no statistically significant difference between umeclidinium and glycopyrronium for this outcome (difference: 0.03 L [95% CI, –0.01 to 0.06; $P = 0.136$]).

Week 24

Umeclidinium versus tiotropium

In the ITC between umeclidinium and tiotropium, eight trials (one umeclidinium trial and seven tiotropium trials) reported data on this outcome at week 24. There was no statistically significant heterogeneity across the tiotropium trials ($I^2 = 33.2\%$; $P = 0.175$). The pooled estimates of trough FEV_1 at week 24 in the seven tiotropium trials were comparable with those in the umeclidinium trial, and the between-group difference was not statistically or clinically significant (difference: 0 [95% CI, –0.04 to 0.05; $P = 0.854$]).

Umeclidinium versus aclidinium bromide

Results from two studies (one umeclidinium trial and one aclidinium bromide trial) were combined without conducting a meta-analysis. Testing for heterogeneity was not performed. The findings indicated that there was no statistically significant difference between umeclidinium and aclidinium bromide for this outcome (difference: –0.01 L [95% CI, –0.07 to 0.05; $P = 0.663$]).

Umeclidinium versus glycopyrronium

Four studies (one umeclidinium trial and three glycopyrronium trials) reported data on this outcome at week 24. The glycopyrronium trials synthesized by meta-analysis were statistically homogeneous ($I^2 = 0$; $P = 0.701$). ITC results indicated that there was no statistically significant difference between umeclidinium and glycopyrronium for this outcome (difference: –0.01 L [95% CI, –0.05 to 0.04; $P = 0.777$]).

None of these between-group differences are considered clinically relevant according to the generally accepted MCID of 0.10 L for FEV_1. Details are presented in Table 25.

TABLE 25: TROUGH FORCED EXPIRATORY VOLUME IN ONE SECOND AT WEEK 12 AND WEEK 24 (LITRES), INDIRECT TREATMENT COMPARISON RESULTS

	Comparator Treatment	Reference Treatment
		Placebo
Trough FEV_1 at week 12 (mean difference from baseline, 95% CI)	UMEC	0.14 (0.10, 0.17), favouring UMEC
	TIO	0.12 (0.10, 0.14), favouring TIO
	ITC between UMEC and TIO: 0.02 (–0.02 to 0.06); *P* = 0.341	
	UMEC	0.14 (0.10, 0.17), favouring UMEC
	AC	0.10 (0.07, 0.13), favouring AC
	ITC between UMEC and AC: 0.04 (–0.01 to 0.08); *P* = 0.108	
	UMEC	0.14 (0.10, 0.17), favouring UMEC
	GLYCO	0.11 (0.09, 0.13), favouring GLYCO
	ITC between UMEC and GLYCO: 0.03 (–0.01 to 0.06); *P* = 0.136	
Trough FEV_1 at week 24 (mean difference from baseline, 95% CI)	UMEC	0.12 (0.08, 0.16), favouring UMEC
	TIO	0.11 (0.10, 0.13), favouring TIO
	ITC between UMEC and TIO: 0 (–0.04 to 0.05); *P* = 0.854	
	UMEC	0.12 (0.08, 0.16), favouring UMEC
	AC	0.13 (0.08, 0.17), favouring AC
	ITC between UMEC and AC: –0.01 (–0.07 to 0.05); *P* = 0.663	
	UMEC	0.12 (0.08, 0.16), favouring UMEC
	GLYCO	0.12 (0.10, 0.14), favouring GLYCO
	ITC between UMEC and GLYCO: –0.01 (–0.05 to 0.04); *P* = 0.777	

AC = aclidinium; CI = confidence interval; FEV_1 = forced expiratory volume in one second; GLYCO = glycopyrronium; ITC = indirect treatment comparison; TIO = tiotropium; UMEC = umeclidinium.
Source: Manufacturer-submitted indirect treatment comparison.[47]

b) Change from baseline for St. George's Respiratory Questionnaire total score

Week 12

Umeclidinium versus tiotropium

Six trials (two umeclidinium trials and four tiotropium trials) assessed SGRQ total score at week 12. There was no statistically significant heterogeneity across the umeclidinium trials or the tiotropium trials (umeclidinium trials: I^2 = 68.0%, *P* = 0.077; tiotropium trials: I^2 = 44.5%, *P* = 0.144). Results of the ITC indicated that there was no statistically significant difference between umeclidinium and tiotropium for this outcome (difference: –2.65 units [95% CI, –7.09 to 1.79; *P* = 0.242]).

Umeclidinium versus aclidinium bromide

Two umeclidinium trials and three aclidinium bromide trials reported data on SGRQ total score at week 12. There was no statistically significant heterogeneity between the umeclidinium trials or the aclidinium bromide trials (umeclidinium trials: I^2 = 68.0%, *P* = 0.077; aclidinium bromide trials: I^2 = 46.6%, *P* = 0.154). Findings from the ITC suggested that there was no statistically significant difference between umeclidinium and aclidinium bromide for this outcome (difference: –2.68 units [95% CI, –7.12 to 1.75, *P* = 0.235]).

Umeclidinium versus glycopyrronium

Data from two umeclidinium trials and one glycopyrronium trial were included in the ITC for this outcome at week 12. There was no statistically significant heterogeneity between the umeclidinium trials (I^2 = 68.0%, *P* = 0.077). Findings from this ITC suggested that there was no statistically significant difference between umeclidinium and glycopyrronium on the SGRQ total score at week 12 (difference: –2.15 units [95% CI, –6.60 to 2.31; *P* = 0.345]).

Week 24

Umeclidinium versus tiotropium

In the ITC between umeclidinium and tiotropium, one umeclidinium trial and seven tiotropium trials were identified in the systematic review that reported this outcome at week 24. There was no statistically significant heterogeneity detected across the tiotropium trials (I^2 = 20.9%, *P* = 0.270). Findings from this ITC showed that there was no statistically significant difference between umeclidinium and tiotropium for this outcome (difference: –2.32 units [95% CI, –4.78 to 0.15; *P* = 0.066]).

Umeclidinium versus aclidinium bromide

Data from one umeclidinium trial and one aclidinium bromide trial were used in the ITC between umeclidinium and aclidinium bromide for this outcome. A statistically significant difference between umeclidinium and aclidinium bromide was not observed in this ITC (difference: –0.09 units [95% CI, –3.30 to 3.12; *P* = 0.956]).

Umeclidinium versus glycopyrronium

Data from one umeclidinium trial and three glycopyrronium trials were included in the ITC between umeclidinium and glycopyrronium for this outcome at week 24. There was no statistically significant heterogeneity detected across the glycopyrronium trials (I^2 = 0, *P* = 0.548). Findings from this ITC suggested that there was no statistically significant difference between umeclidinium and glycopyrronium on the SGRQ total score at week 24 (difference: –1.98 units [95% CI, –4.61 to 0.65; *P* = 0.141]).

A lower SGRQ score indicates better HRQoL. None of the between-group differences exceeded the MCID for SGRQ total score (4 units). Details are presented in Table 26.

TABLE 26: 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
		Placebo
Between-group difference in SGRQ score at week 12 (mean difference from baseline, 95% CI)	UMEC	–5.32 (–9.46 to –1.18), favouring UMEC
	TIO	–2.67 (–4.27 to –1.07), favouring TIO
	ITC between UMEC and TIO: –2.65 (–7.09 to 1.79); *P* = 0.242	
	UMEC	–5.32 (–9.46 to –1.18), favouring UMEC
	AC	–2.63 (–4.22 to –1.05), favouring AC
	ITC between UMEC and AC: –2.68 (–7.12 to 1.75); *P* = 0.235	
	UMEC	–5.32 (–9.46 to –1.18), favouring UMEC
	GLYCO	–3.17 (–4.82 to –1.52), favouring GLYCO
	ITC between UMEC and GLYCO: –2.15 (–6.60 to 2.31); *P* = 0.345	
Between-group difference in SGRQ score at week 24 (mean difference from baseline, 95% CI)	UMEC	–4.69 (–7.07 to –2.31), favouring UMEC
	TIO	–2.37 (–3.02 to –1.72), favouring TIO
	ITC between UMEC and TIO: –2.32 (–4.78 to 0.15); *P* = 0.066	
	UMEC	–4.69 (–7.07 to –2.31), favouring UMEC
	AC	–4.60 (–6.76 to –2.44), favouring AC
	ITC between UMEC and AC: –0.09 (–3.30 to 3.12); *P* = 0.956	
	UMEC	–4.69 (–7.07 to –2.31), favouring UMEC
	GLYCO	–2.71 (–3.83 to –1.60), favouring GLYCO
	ITC between UMEC and GLYCO: –1.98 (–4.61 to 0.65); *P* = 0.141	

AC = aclidinium; CI = confidence interval; GLYCO = glycopyrronium; ITC = indirect treatment comparison; SGRQ = St. George's Respiratory Questionnaire; TIO = tiotropium; UMEC = umeclidinium.
Source: Manufacturer-submitted indirect treatment comparison.[47]

c) Treatment dyspnea index focal score

Week 12

Umeclidinium versus tiotropium

In the ITC between umeclidinium and tiotropium, two umeclidinium trials and five tiotropium trials were identified in the systematic review that reported this outcome at week 12. There was no statistically significant heterogeneity between the umeclidinium trials or the tiotropium trials (umeclidinium trials: $I^2 = 0$, $P = 0.858$; tiotropium trials: $I^2 = 0$, $P = 0.339$). There was no statistically significant difference between umeclidinium and tiotropium for this outcome (difference: 0.19 units [95% CI, –0.29 to 0.67; $P = 0.434$]).

Umeclidinium versus aclidinium bromide

Two umeclidinium trials and three aclidinium bromide trials reported data on this outcome at week 12; therefore, they were included in this ITC. There was no statistically significant heterogeneity between the umeclidinium trials or the aclidinium bromide trials (umeclidinium trials: $I^2 = 0$, $P = 0.858$; aclidinium bromide trials: $I^2 = 0$, $P = 0.947$). There was no statistically significant between-group difference for umeclidinium versus aclidinium bromide (difference: –0.05 units [95% CI, –0.56 to 0.46; $P = 0.851$]).

Umeclidinium versus glycopyrronium

Data from two umeclidinium trials and two glycopyrronium trials were included in the ITC between umeclidinium and glycopyrronium for this outcome at week 12. There was no statistically significant heterogeneity between the umeclidinium trials or the glycopyrronium trials (umeclidinium trials: $I^2 = 0$, $P = 0.858$; glycopyrronium trials: $I^2 = 0$, $P = 0.561$). Findings from this ITC suggested that there was no statistically significant difference between umeclidinium and glycopyrronium on the TDI focal score at week 12 (difference: 0.21 units [95% CI, –0.33 to 0.75; $P = 0.448$]).

Week 24

Umeclidinium versus tiotropium

In the ITC between umeclidinium and tiotropium, one umeclidinium trial and five tiotropium trials were included. There was no statistically significant heterogeneity across the tiotropium trials ($I^2 = 0$; $P = 0.735$). There was no statistically significant between-group difference for umeclidinium versus tiotropium (difference: 0.15 units [95% CI, –0.39 to 0.70; $P = 0.578$]).

Umeclidinium versus aclidinium bromide

One umeclidinium trial and one aclidinium bromide trial reported data on TDI focal score at week 24. Findings from these two studies suggested that there was no statistically significant difference between umeclidinium and aclidinium bromide for this outcome (difference: 0 [95% CI, –0.77 to 0.77; $P = 1.000$]).

Umeclidinium versus glycopyrronium

Data from one umeclidinium trial and three glycopyrronium trials were included in the ITC between umeclidinium and glycopyrronium for this outcome at week 24. There was no statistically significant heterogeneity across the glycopyrronium trials ($I^2 = 0$; $P = 0.796$). Findings from this ITC suggested that there was no statistically significant difference between umeclidinium and glycopyrronium on the TDI focal score at week 24 (difference: 0.08 units [95% CI, –0.49 to 0.65; $P = 0.786$]).

None of these between-group differences are considered clinically relevant according to the MCID in TDI score (1 unit). Details are presented in Table 27.

TABLE 27: CHANGE FROM BASELINE FOR TREATMENT DYSPNEA INDEX FOCAL SCORE AT WEEK 12 AND WEEK 24, INDIRECT TREATMENT COMPARISON RESULTS

	Comparator treatment	Reference treatment
		Placebo
Between-group differences in TDI focal score at week 12 (mean difference from baseline, 95% CI)	UMEC	0.92 (0.51 to 1.33), favouring UMEC
	TIO	0.73 (0.48 to 0.97), favouring TIO
	ITC between UMEC and TIO: 0.19 (–0.29 to 0.67); *P* = 0.434	
	UMEC	0.92 (0.51 to 1.33), favouring UMEC
	AC	0.97 (0.66 to 1.27), favouring AC
	ITC between UMEC and AC: –0.05 (–0.56 to 0.46); *P* = 0.851	
	UMEC	0.92 (0.51 to 1.33), favouring UMEC
	GLYCO	0.71 (0.34 to 1.08), favouring GLYCO
	ITC between UMEC and GLYCO: 0.21 (–0.33 to 0.75); *P* = 0.448	
Between-group differences in TDI focal score at week 24 (mean difference from baseline, 95% CI)	UMEC	1 (0.5 to 1.5), favouring UMEC
	TIO	0.85 (0.64 to 1.06), favouring TIO
	ITC between UMEC and TIO: 0.15 (–0.39 to 0.70); *P* = 0.578	
	UMEC	1.0 (0.5 to 1.5), favouring UMEC
	AC	1.0 (0.41, 1.59), favouring AC
	ITC between UMEC and AC: 0 (–0.77 to 0.77); *P* = 1.0	
	UMEC	1.0 (0.5 to 1.5), favouring UMEC
	GLYCO	0.92 (0.64 to 1.20), favouring GLYCO
	ITC between UMEC and GLYCO: 0.08 (–0.49 to 0.65); *P* = 0.786	

AC= aclidinium; CI = confidence interval; GLYCO = glycopyrronium; ITC = indirect treatment comparison; TDI = Transition Dyspnea Index; TIO = tiotropium; UMEC= umeclidinium.
Data source: Manufacturer-submitted indirect treatment comparison.[47]

c) Rescue medication use (puffs/day)

Week 12

Umeclidinium versus tiotropium

Two umeclidinium trials and one tiotropium trial reported data on this outcome at week 12; therefore, they were included in the ITC of umeclidinium versus tiotropium. There was no statistically significant heterogeneity between the umeclidinium trials ($I^2 = 0$, $P = 0.360$). The difference between umeclidinium and tiotropium was not statistically significant (difference: –0.35 puffs/day [95% CI, –0.97 to 0.26; $P = 0.262$]).

Week 24

Umeclidinium versus tiotropium

One umeclidinium trial and two tiotropium trials reported data on this outcome at week 24. There was no statistically significant heterogeneity between the tiotropium trials ($I^2 = 0$; $P = 0.456$).The pooled estimates of the number of rescue medication use per day at week 24 were comparable between the umeclidinium trial and the tiotropium trials, and the between-group difference was not statistically significant (difference: 0.20 puffs/day [95% CI, –0.36 to 0.75; $P = 0.491$]).

Umeclidinium versus glycopyrronium

Data from one umeclidinium trial and two glycopyrronium trials were included in the ITC between umeclidinium and glycopyrronium for this outcome at week 24. There was no statistically significant heterogeneity between the glycopyrronium trials ($I^2 = 0$, $P = 0.498$). Findings from this ITC suggested that there was no statistically significant difference between umeclidinium and glycopyrronium on daily rescue medication use at week 24 (difference: 0.08 puffs/day [95% CI, –0.47 to 0.63; $P = 0.765$]).

It is unclear whether these between-group differences are clinically significant. Details are presented in Table 28.

TABLE 28: RESCUE MEDICATION USE (NUMBER OF PUFFS/DAY) AT WEEK 12 AND WEEK 24, INDIRECT TREATMENT COMPARISON RESULTS

	Comparator Treatment	Reference Treatment
		Placebo
Rescue medication use at week 12 (mean difference from baseline in number of puffs/day, 95% CI)	UMEC	–0.48 (–0.86 to –0.11), favouring UMEC
	TIO	–0.13 (–0.62 to 0.36), favouring TIO
	ITC between UMEC and TIO: –0.35, (–0.97 to 0.26); *P* = 0.262	
	UMEC	No network
	AC	
	ITC between UMEC and AC: NA	
	UMEC	No network
	GLYCO	
	ITC between UMEC and GLYCO: NA	
Rescue medication use at week 24 (mean difference from baseline in number of puffs/day, 95% CI)	UMEC	–0.3 (–0.8 to 0.2), favouring UMEC
	TIO	–0.50 (–0.74 to –0.25), favouring TIO
	ITC between UMEC and TIO: 0.20 (–0.36 to 0.75); *P* = 0.491	
	UMEC	No network
	AC	
	ITC between UMEC and AC: NA	
	UMEC	–0.3 (–0.8 to 0.2), favouring UMEC
	GLYCO	–0.38 (–0.62 to –0.15), favouring GLYCO
	ITC between UMEC and GLYCO: 0.08 (–0.47 to 0.63); *P* = 0.765	

AC = aclidinium; CI = confidence interval; GLYCO = glycopyrronium; ITC = indirect treatment comparison; NA = not applicable; TIO = tiotropium; UMEC = umeclidinium.
Data source: Manufacturer-submitted indirect treatment comparison.[47]

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.[49] Details and commentary for each of the relevant items identified by the ISPOR group are provided in Table 29.

Limitations

Only a high-level summary of methods and results of the ITC was provided in the manufacturer submission. The lack of details led to the following concerns:

- Trial characteristics and patient characteristics at baseline were provided in the ITC. However, insufficient details were reported with respect to some 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.

Clinical heterogeneity was assessed by comparing various factors such as study design, exacerbations, smoking status, background treatment with ICS and/or LABA, and patients' baseline characteristics. These results were presented descriptively. The treatment duration and patient baseline characteristics varied substantially across the included studies of long-acting bronchodilators. The impact of such heterogeneity on the results of the ITC was not explored further, for example by performing subgroup analyses. In the manufacturer's comment on this clinical review, it was indicated that the results of the sensitivity analysis (conducted by excluding studies where the background LABA treatment was allowed for the comparison between umeclidinium and tiotropium) showed that the magnitude of the treatment effect on trough FEV_1 at weeks 12 and 24 changed; however, the conclusion remained unchanged.[48] In addition, there was no information with respect to publication bias determination. COPD was defined using the GOLD guidelines, but the severity of disease was not reported. Therefore, we were not able to determine the consistency of disease severity across trials.

A number of key outcomes identified in the CDR systematic review were not evaluated in the ITC. These included COPD exacerbations, exercise tolerance, and safety outcomes. According to the CTS and GOLD committee, the goals of COPD treatment are to reduce symptoms and reduce the risk of future events (i.e., prevent disease progression, prevent exacerbations, and reduce mortality). These gaps limit the ability to assess the comparative benefit and harms of umeclidinium versus other long-acting bronchodilator monotherapies.

Results of the risk of bias assessment suggested that most studies had a low risk of bias; however, four studies were identified as having a high risk of bias due to the open-label study design or imbalances in baseline patient characteristics, in spite of randomization.[48]

Strengths

A systematic literature search was performed and a search strategy was provided to ensure the comprehensiveness and transparency of data retrieval. Risk of bias of the included studies was assessed. Scenario analysis was conducted to provide additional information to the base-case analysis regarding the clinical effectiveness of the study drugs in different scenarios.

TABLE 29: APPRAISAL OF THE INDIRECT COMPARISON ANALYSES USING INTERNATIONAL SOCIETY FOR PHARMACOECONOMICS AND OUTCOMES RESEARCH CRITERIA[49]

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. • Quality assessment of the included studies was conducted; methods or results were not provided in the original submission by the manufacturer, but were provided in the manufacturer's comments on the current review.
3. Are the outcome measures described?	• Outcomes assessed in the indirect comparison analysis were described.
4. Is there a description of methods for analysis/synthesis of evidence? • Description of analyses methods/models • Handling of potential bias/inconsistency • Analysis framework	• ITC using the Bucher approach was on the outcomes of interest. Random-effects models were used in data synthesis. • Statistical and clinical heterogeneity were examined. • It was not clear whether publication bias was examined; methods or results were not provided.
5. Are sensitivity analyses presented?	• Sensitivity analyses were performed for the comparison between UMEC and TIO only, for one outcome. Results were briefly provided in the manufacturer's comment on this current clinical review, but not in the original submission by the manufacturer.
6. Do the results include a summary of the studies included in the network of evidence? • Individual study data? • Network of studies?	• Tables of trial characteristics and patient baseline characteristics of all included studies were provided. • Figures showing the network of studies were provided. Forest plots of meta-analysis results between each of the active comparators and the reference treatment (placebo) 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?	• Not applicable
8. Are the results of the evidence synthesis presented clearly?	• The results of the analysis were clearly reported for each outcome measure: point estimates and 95% confidence intervals and probability values as measures of uncertainty.
9. Sensitivity/scenario analyses	• Scenario analysis was reported.

ITC = indirect treatment comparison; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; RCT = randomized controlled trial; TIO = tiotropium; UMEC = umeclidinium.

Based on the ISPOR appraisal tool, the ITC provided by the manufacturer satisfied most of the items on the checklist, except for publication bias detection.

4. Summary

The manufacturer undertook a systematic review of RCTs and performed an indirect treatment analysis using the Bucher method to compare umeclidinium with other LAMA monotherapies. The results suggested that umeclidinium was not statistically different from tiotropium, aclidinium bromide, or glycopyrronium in improving lung function (as measured by change in FEV_1), reducing the need for rescue medication use, improving HRQoL, and improving dyspnea symptoms for patients with COPD; the observed between-group differences were not clinically meaningful according to the respective MCIDs. Given that no head-to-head trials comparing long-acting bronchodilator therapies were identified, and considering the clinical heterogeneity across the included trials, the results of the ITC should be interpreted with caution. Since other efficacy and safety outcomes were not evaluated in this ITC, we are not able to estimate the other clinical benefits and risks for umeclidinium relative to other comparators.

APPENDIX 6: VALIDITY OF OUTCOME MEASURES

Aim

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

- Forced expiratory volume in one second (FEV_1)
- St. George's Respiratory Questionnaire (SGRQ)
- Transition Dyspnea Index (TDI)
- Exercise endurance time (EET).

Findings

Evidence of validity and MCID for FEV_1, SGRQ, TDI, and EET are briefly summarized in Table 30.

TABLE 30: VALIDITY AND MINIMAL CLINICALLY IMPORTANCE DIFFERENCES 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 1 second.	Yes	0.10 L to 0.14 L, or a change of 5% to 10% from baseline	Cazzola 2008[36] Jones 2014[42]
SGRQ	SGRQ is a disease-specific measure of HRQoL that consists of 50 items with 76 responses. It was developed for patients with chronic airflow limitation. The questionnaire is divided into three dimensions: Symptoms, Activity, and Impacts of the disease. The total score ranges from 0 to 100, where 0 indicates no impairment and 100 indicates greatest impairment.	Yes	4 units	Jones 1992[50] Leidy 2010[51] Meguro 2007[52] Maly 2006[53]
TDI	TDI is used to measure dyspnea, and consists of 24 items measuring three categories: functional impairment, magnitude of task, and magnitude of effort. Items are rated in 7 grades ranging from –3 (major deterioration) to +3 (major improvement), where lower scores indicate more deterioration in the severity of dyspnea from baseline.	Yes	1 unit	American Thoracic Society[54]
EET	EET was measured using the ESWT, which is a standardized constant-paced field test for the assessment of endurance capacity in patients with chronic lung disease.	Unknown	70 secs (95% CI, 46 to 95) 65 secs (95% CI, 45 to 85)	Brouillard 2008[55] Eaton 2006[56] Brouillard 2007[57] Troosters 2013[58] Pepin 2011[59]

CI = confidence interval; EET = exercise endurance time; ESWT = endurance shuttle walk test; FEV_1 = forced expiratory volume in one second; HRQoL = health-related quality of life; MCID = minimal clinical important difference; secs = seconds; SGRQ = St. George 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. It is commonly used in both clinical practice and clinical trials, and is generally thought to correlate with chronic obstructive pulmonary disease (COPD) outcomes.[37,60] In clinical practice, FEV_1 is used to grade risk of death in COPD patients.[61] 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.[36,42] Previous research indicated that relative change rather than absolute change may be more meaningful in patients with worse airflow limitation.[42] There is evidence that for patients who are undergoing a COPD exacerbation, a two-day increase of 0.10 L reduced the relative risk of treatment failure by 20%.[60] A systematic review published in 2011 investigated the relationship between change in FEV_1 and patient-reported outcomes using data from RCTs of long-acting bronchodilator therapies.[38] Findings suggested that change in trough FEV_1 was negatively correlated with change in the SGRQ total score: a 0.10 L increase in trough FEV_1 was associated with a statistically significant reduction of 2.5 units in the SGRQ total score, while a change of four units in the SGRQ total score was related to a 0.16 L increase in FEV_1. Change in FEV_1 had weak associations with TDI and COPD exacerbations: a 0.10 L increase in FEV_1 was associated with a 0.5 unit improvement in TDI, or a 6% reduction in the proportion of patients experiencing at least one exacerbation.

While both pre- and post-bronchodilator FEV_1 values have been reported to be indicators of health status, risk of death, and level of COPD severity, the Global Initiative for Chronic Lung Disease (GOLD) criteria indicate that post-bronchodilator values should be used.[61] 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.[61] 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 a post-bronchodilator than with pre-bronchodilator per cent predicted FEV_1 ($P = 0.009$ versus 0.131).

St. George's Respiratory Questionnaire

The SGRQ is a disease-specific measure of health-related quality of life (HRQoL) that was specifically developed for patients with airway obstruction.[50] 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.[62] The instrument has been used worldwide in studies and in clinical settings.[62] 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 or facing challenges with employment and recreational activities (which are indicative of social impact).[63]

The questionnaire contains 50 items and 76 weighted responses that are divided into three subscales: Symptoms (8 items measuring the frequency of respiratory symptoms over a preceding period that may range from one month to one year); Activity (16 items measuring the disturbances to patients' daily physical activity); and Impacts (26 items measuring the psychosocial impact of the disease).[53,64,65] Items are weighted using empirically derived weights in order to determine the SGRQ total score, which ranges from 0 to 100, where 0 indicates no impairment and 100 indicates worst possible health.[52,53] The generally accepted MCID for a change in total SGRQ from baseline is 4 units, and a decrease in score

indicates an improvement in HRQoL.[51,64] In the manual of the SGRQ-C questionnaire (a shorter version of SGRQ that was developed using COPD data only and specific to patients with COPD), an MCID of 4 units is used for both the within-group comparison, as well as the between-group comparison.[66] The SGRQ manual does not indicate whether the MCID of four units can be used in the between-group comparison. However, it is reasonable to use this threshold to determine the clinical significance of the differences between groups of patients.

Component scores for the Symptoms, Activity, and Impacts domains can be calculated (also ranging from 0 to 100) in addition to the total score. In the Symptoms domain, patients are asked to rate the appearance, frequency, and severity of respiratory symptoms (wheezing, breathlessness, coughing, etc.) on a five-point scale, where low scores indicate no symptoms and high scores indicate more severe symptoms.[53] A number of items in the Symptoms component relate to the frequency of symptoms over the previous year.[67] 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.[53] 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 obstructive airways disease (employment, panic, medication, and side effects).[67]

Transition Dyspnea Index

TDI is an interviewer-administered, multi-dimensional instrument used to measure the severity of dyspnea.[54,68] It was developed by Mahler et al. in 1984. When used to determine breathlessness in patient at baseline, it is called the Baseline Dyspnea Index (BDI). The TDI measures changes in dyspnea severity from baseline as established by the BDI. Both the BDI and TDI consist of 24 items in three categories: functional impairment, magnitude of task, and magnitude of effort, assessed in the BDI, and the changes in functional impairment, magnitude of task, and magnitude of effort from baseline in the TDI.

At baseline, dyspnea is rated by items in the 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. A 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 the BDI and TDI have been demonstrated in previous clinical trials.[69] A 1-unit change in TDI is considered to be the MCID.[54]

Exercise endurance time

The European Medicines Agency (EMA) stated that when lung function is selected as a primary end point, a co-primary end point (such as assessment of exercise capacity) should be evaluated to provide additional evidence of efficacy.[2] In the studies included in this 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.[55,56]

Before each ESWT, patients received standardized instructions to walk for as long as possible, although there was a predetermined 20-minute maximum. No encouragement was to 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 course. The course was identified by two cones, each positioned 0.5 metres from either end to allow patients to walk in an oval and thereby avoid the need for abrupt changes in direction. After a 90-second warm-up, the 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.[55] 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 or 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.[57] A difference of 65 seconds (95% CI, 45 seconds to 85 seconds) was suggested as the MCID for EET in more recent clinical studies.[59]

Summary

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

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

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