CADTH

CADTH Common Drug Review

Clinical Review Report

FLUTICASONE FUROATE/UMECLIDINIUM/VILANTEROL (TRELEGY ELLIPTA)

(GlaxoSmithKline plc)

Indication: Long-term, once daily, maintenance treatment of chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema in patients who are not adequately treated by a combination of an ICS/LABA

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Abbreviations

ACO	Asthma-COPD overlap
BDI	Baseline Dyspnea Index
BUD	budesonide
CAT	COPD assessment test
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CTS	Canadian Thoracic Society
EQ-5D-5L	EuroQol 5-Dimensions 5-Levels questionnaire
EXACT-RS	EXAcerbations of Chronic Pulmonary Disease Tool – Respiratory Symptoms
FEV_1	forced expiratory volume in one second
FF	fluticasone furoate
FOR	formoterol fumarate
FVC	forced vital capacity
GOLD	Global initiative for chronic Obstructive Lung Disease
HR	hazard ratio
HRQL	health-related quality of life
ICS	inhaled corticosteroid
IDC	indirect comparison
ITT	intention to treat
LABA	long-acting beta2-agonists
LAMA	long-acting muscarinic antagonist
LS	least squares
MCID	minimal clinically important difference
MMRM	mixed model repeated measures
NMA	network meta-analysis
RCT	randomized controlled trial
SGRQ	St. George's Respiratory Questionnaire
SGRQ-C	St. George's Respiratory Questionnaire for COPD patients
TDI	Transition Dyspnea Index
UMEC	Umeclidinium
URTI	upper respiratory tract infections
VAS	visual analogue scale
VI	vilanterol

Drug	Fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta)
Indication	For long-term, once daily, maintenance treatment of chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema in patients who are not adequately treated by a combination of an ICS/LABA
Reimbursement Request	Fluticasone furoate/umeclidinium/vilanterol should be recommended where the following clinical criteria are met: • moderate to severe COPD as defined by spirometry; and • at risk of exacerbations despite a long-acting bronchodilator (LAMA or LABA); or • symptomatic or at risk of exacerbations despite a LAMA/LABA or ICS/LABA; or • currently on a LAMA/ICS/LABA.
Dosage Form(s)	Inhalation
NOC Date	April 4, 2018
Manufacturer	GlaxoSmithKline plc

Executive Summary

Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable respiratory illness that includes chronic bronchitis and emphysema.[1,2] COPD is commonly caused by smoking; an estimated 80% to 90% of COPD cases are attributed to it.[1] COPD is characterized by progressive, partially reversible, airway obstruction and lung hyperinflation, systemic manifestations, and increasing frequency and severity of exacerbations.[1] COPD is an underdiagnosed illness; thus, prevalence statistics are likely to underestimate the number of people currently living with COPD. In Canada, COPD is the fourth-leading cause of death.[1] According to a Statistics Canada report based on data from 2012 to 2015, it is estimated that 12% of Canadians aged 35- to 79-years-old have a measured airflow obstruction consistent with COPD.[3] Patients with COPD often experience negative consequences that impact their day-to-day lives including their ability to breathe, talk, sleep, work, and socialize. Overall, these patient experiences describe a physically and mentally exhausting disorder that can result in anxiety, depression, and decreased quality of life. The goals of COPD management are to prevent disease progression, reduce the frequency and severity of exacerbations, alleviate symptoms, improve exercise tolerance and daily activity, treat exacerbations and complications, improve health status, and reduce mortality.[4] Management decisions are guided by disease severity (i.e., symptoms/disability and spirometry) and the frequency of acute exacerbations. Smoking cessation is the single most effective intervention to reduce the risk of developing COPD and the only intervention shown to slow the rate of lung function decline.[1] Bronchodilators form the mainstay of pharmacotherapy for COPD,[1] and include long-acting beta-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs). Muscarinic antagonists and beta-agonist drugs used in combination as a step-up therapy is recommended for patients with stable COPD with exacerbations despite the use of LAMA or LABA therapy.[5] According to the Canadian Thoracic Society, based on consensus, step-up to triple therapy where LAMA plus inhaled corticosteroid (ICS)/LABA are used may be considered in stable COPD with high-symptom burden and poor health status despite the use of an inhaled LAMA plus LABA dual therapy.[5]

Trelegy Ellipta is the first triple combination therapy consisting of an ICS, fluticasone furoate (FF); a LABA, vilanterol, (VI); and a LAMA, umeclidinium (UMEC).[6] FF, the ICS component, is a synthetic trifluorinated corticosteroid with potent, local, anti-inflammatory activity, whereas the LABA and LAMA components act as long-acting bronchodilators via stimulation of the beta2 receptors and competitive inhibition of muscarinic receptors, respectively. This triple therapy is administered once daily as a dry powder for oral inhalation via the Ellipta inhaler. Each of the Trelegy Ellipta components is available in other formulations, which also have Health Canada–approved indications for the management of COPD.

The objective of this review was to perform a systematic review of the beneficial and harmful effects of FF/UMEC/VI (Trelegy Ellipta; 100/62.5/25 mcg) for the treatment of patients with COPD, including chronic bronchitis and/or emphysema, who have moderate to severe COPD and are symptomatic and/or at risk of exacerbations despite the use of maintenance therapy with a LAMA, ICS/LABA, or LAMA/LABA, or are currently on a LAMA/ICS/LABA.

Results and Interpretation

Included Studies

Three phase III randomized controlled trials (RCTs) identified as pivotal trials by the manufacturer (FULFIL[7], IMPACT[8], and Study 200812[9]) were included in this review. The primary objective of FULFIL was to evaluate the effects of FF/UMEC/VI on lung function and health-related quality of life compared with budesonide/formoterol (BUD/FOR) after 24 weeks of treatment. In FULFIL, patients were randomized in a 1:1 ratio for treatment with FF/UMEC/VI 100/62.5/25 mcg via the Ellipta once daily and placebo via the Turbuhaler twice daily, or treatment with BUD/FOR 400/12 mcg via the Turbuhaler twice daily and placebo via the Ellipta once daily. A subset of patients could continue in their assigned treatment groups into an extension study to receive a total of 52 weeks of treatment. The primary objective of IMPACT was to evaluate the efficacy of FF/UMEC/VI to reduce the annual rate of combined moderate and severe exacerbations compared with dual therapy of FF/VI or UMEC/VI in patients with COPD. In the 52-week IMPACT trial, patients were randomized in a 2:2:1 ratio for once daily treatment via the Ellipta with FF/UMEC/VI 100/62.5/25 mcg, FF/VI 100/25 mcg, or UMEC/VI 62.5/25 mcg, respectively. Study 200812 aimed to compare the effect of FF/UMEC/VI with FF/VI+UMEC on lung function after 24 weeks of treatment. In this 24-week trial, patients were assigned to study arms in a 1:1 ratio for treatment with FF/UMEC/VI 100/62.5/25 mcg via the Ellipta once daily and placebo via the Ellipta once daily in the morning, or treatment with FF/VI 100/25 mcg via the Ellipta once daily in the morning and UMEC 62.5 mcg via the Ellipta once daily in the morning. Two additional 12-week, double-blind, placebo-controlled, multi-centre, parallel-group studies designed to assess the efficacy and safety of UMEC added to FF/VI in patients with COPD were reviewed in the Appendices of this report. As well, a manufacturer-provided indirect comparison of FF/UMEC/VI versus other triple therapies is summarized and critically appraised in Appendix 8.

All three trials were similar in inclusion and exclusion criteria, and recruited patients 40 years of age and older who were former or current smokers, had a diagnosis of COPD, a score of 10 or more on the COPD assessment test (CAT), and a post-salbutamol forced expiratory volume in one second (FEV_1)/ forced vital capacity (FVC) ratio of less than 0.70. The only difference in inclusion criteria related to FEV_1 and exacerbation history. FULFIL required

either a post-bronchodilator FEV_1 of less than 50% predicted normal, or a post-bronchodilator FEV_1 of less than 80% predicted normal and a documented history of two or more moderate exacerbations or one severe (hospitalized) exacerbation in the previous year. In contrast, both IMPACT and Study 200812 required either a post-bronchodilator FEV_1 of less than 50% predicted normal and a documented history of one or more moderate or severe COPD exacerbation in the previous 12 months, or a post-bronchodilator FEV_1 of greater than or equal to 50% and less than 80% of the predicted normal and a documented history of two or more moderate exacerbations or a documented history of one or more severe (hospitalized) COPD exacerbation in the previous year.

Whereas the studies were generally well-designed, the statistical analysis of the secondary outcome measures in FULFIL was not adjusted for multiplicity; there was a risk of type I error for these outcomes, which limits the ability to draw conclusions. The rate of COPD exacerbations is a key outcome for patients, yet only one of the studies (IMPACT) was designed to evaluate exacerbations as a primary outcome. The comparators used two of the three studies were components of FF/UMEC/VI, while ICS/LABA was the comparator in the third study (FULFIL). Therefore, there is limited data comparing FF/UMEC/VI with LAMA/LABA combinations (other than UMEC/VI) and with other triple therapies for COPD.

Efficacy

Pulmonary function was assessed using FEV_1. The change from baseline in trough FEV_1 was evaluated as a co-primary outcome (at week 24) in FULFIL, the primary outcome (at week 24) in Study 200812, and as a secondary outcome (at week 52) in IMPACT. Symptoms (including those related to pulmonary function) were identified as important based on the patient input. In FULFIL, the change from baseline in trough FEV_1 at 24 weeks for FF/UMEC/VI compared with BUD/FOR, was 0.17 L (95% confidence interval [CI], 0.15 L to 0.19 L; $P < 0.001$). The improvement in FEV_1 was statistically and clinically significant (minimal clinically important difference [MCID] = 0.10 L to 0.14 L). In IMPACT, the difference in least squares change from baseline in trough FEV_1 at 52 weeks for FF/UMEC/VI compared with FF/VI was 0.097 L (95% CI, 0.085 L to 0.109 L), and compared with UMEC/VI was 0.054 L (95% CI, 0.039 L to 0.069 L). The improvement in FEV_1 was statistically significant ($P < 0.001$) but not clinically relevant (MCID = 0.10 L to 0.14 L) for FF/UMEC/VI compared with both FF/VI and UMEC/VI. In Study 200812, the difference in least squares change from baseline in trough FEV_1 at 24 weeks for FF/UMEC/VI compared with FF/VI + UMEC was 0.018 L (95% CI, −0.013 L to 0.050 L) for the modified per-protocol (adherent) population, and 0.026 L (95% CI, −0.002 L to 0.053 L) in the intention-to-treat (ITT) population. The improvement in FEV_1 for FF/UMEC/VI compared with FF/VI + UMEC/VI was noninferior, as the lower bound of the two-sided 95% CI around the treatment difference was above −0.050 L.

The annual rate of on-treatment moderate and severe exacerbations was evaluated as a primary outcome in IMPACT and a secondary outcome in FULFIL. Across all trials, the time to first moderate or severe COPD exacerbation was assessed as a secondary or “other” outcome. Exacerbations were identified as an important outcome based on patient input for this review. In FULFIL, the annualized rate of on-treatment moderate and severe exacerbations during the 24-week study was lower in the FF/UMEC/VI arm than in the BUD/FOR arm (0.22 versus 0.34, respectively) and the rate ratio was 0.65 (95% CI, 0.49 to 0.86). The hazard ratio for time to first on-treatment moderate or severe exacerbation for FF/UMEC/VI compared with BUD at week 24 was 0.67 (95% CI 0.52 to 0.88), and at week 52 for the extension population the hazard ratio was 0.54 (95% CI, 0.35 to 0.83). In

IMPACT, the annualized rate of on-treatment moderate and severe exacerbations during the 52-month study was lower in the FF/UMEC/VI arm than both the FF/VI and UMEC/VI arms (0.91 versus 1.07 and 1.21, respectively); the rate ratios were 0.85 (95% CI, 0.80 to 0.90) and 0.75 (95% CI, 0.70 to 0.81) for comparisons with FF/VI and UMEC/VI, respectively. The hazard ratio (HR) for time to first on-treatment moderate or severe exacerbation for FF/UMEC/VI compared with FF/VI and UMEC/VI at week 52 was 0.85 (95% CI, 0.80 to 0.91) for FF/VI and 0.84 (95% CI, 0.78 to 0.91) for UMEC/VI. In Study 200812, the hazard ratio for time to first on-treatment moderate or severe exacerbation for FF/UMEC/VI compared with FF/VI + UMEC was not statistically significant (HR = 0.87, 95% CI, 0.68 to 1.12).

Health-related quality of life was assessed using the St. George's Respiratory Questionnaire (SGRQ). The change from baseline in SGRQ total score was evaluated as a co-primary outcome in FULFIL, an "other" outcome (at week 52) in IMPACT, and a secondary outcome (at week 24) in Study 200812. Health-related quality of life was determined to be an important outcome based on patient input. In FULFIL, the change from baseline in the SGRQ total score at 24 weeks for FF/UMEC/VI compared with BUD/FOR was −2.2 units (95% CI, −3.5 units to −1.0 units). This difference was not clinically significant (MCID = 4 units). In IMPACT, the difference in least squares change from baseline in the SGRQ total score at 52 weeks for FF/UMEC/VI compared with FF/VI was −1.8 units (95% CI, −2.4 units to −1.1 units; and compared with UMEC/VI, was −1.8 units (95% CI, −2.6 units to −1.0 units); these differences were not considered clinically meaningful (MCID = 4 units). In Study 200812, the difference in least squares change from baseline in the SGRQ total score at 24 weeks for FF/UMEC/VI compared with FF/VI + UMEC was −0.906 units (95% CI, −2.540 units to 0.728 units).

Other efficacy outcomes included COPD-related respiratory symptoms, health status, and the use of rescue medications. However, these outcomes were not adjusted for multiple statistical comparisons and therefore inferences on the associated results should be interpreted with this in mind.

The manufacturer-provided network meta-analysis (NMA) suggested [redacted]. However, unresolved heterogeneity introduces uncertainty into the conclusion that FF/UMEC/VI is comparable in efficacy to other triple therapies in patients with COPD, and data are sparse for some clinically important end points.

Harms

Within each trial, serious adverse events were similar across treatment arms. In FULFIL, at 24 weeks, serious adverse events were reported in 5% and 6% of patients in the FF/UMEC/VI and BUD/FOR arm, respectively. In IMPACT, at 52 weeks, adverse events were reported in 21% to 23% of patients in each arm. In Study 200812, at 24 weeks, adverse events were reported in 10% and 11% of patients in the FF/UMEC/VI and FF/VI + UMEC arm, respectively. The most common severe adverse event was related to

respiratory, thoracic, and mediastinal disorders; COPD; infections and infestations; and pneumonia.

Anticholinergic syndrome affected each arm similarly across trials. In FULFIL, anticholinergic syndrome occurred in 1.8% and 1.9% of patients in the FF/UMEC/VI and BUD/FOR arm, respectively, by week 24. In IMPACT, at week 52, anticholinergic syndrome occurred in 4% of patients in the FF/UMEC/VI arm, and in 3% of patients in both the FF/VI and UMEC/VI arms. In Study 200812, anticholinergic syndrome occurred in 2% and less than 1% in the FF/UMEC/VI and FF/VI + UMEC arms, respectively. Cardiovascular effects affected each arm similarly across trials. In FULFIL, cardiovascular effects occurred in 4.3% and 5.2% of patients in the FF/UMEC/VI and BUD/FOR arm, respectively by week 24. In IMPACT, at week 52, cardiovascular effects occurred in 10% to 11% of patients across trial arms. In Study 200812, cardiovascular effects occurred in 2% and 3% in the FF/UMEC/VI and FF/VI + UMEC arms, respectively. Pneumonia affected each arm similarly across trials, with the exception of BUD/FOR in FULFIL, where pneumonia occurred in 0.8% of patients compared with 2.2% of patients treated with FF/UMEC/VI.

The manufacturer-provided NMA [redacted].

Potential Place in Therapy[1]

International and Canadian recommendations have been reconsidering the approach to COPD management since 2013 to take into consideration new studies and new molecular treatment that have been emerging in the field of COPD management. Decreasing exacerbation rates, especially exacerbation leading to emergency room visits and/or leading to hospitalizations, has been a cornerstone of the therapeutic approach and has been influencing clinical recommendations, in particular in the GOLD (Global initiative for chronic Obstructive Lung Disease) document. Another shift that has been happening is in the way patients are evaluated. Patient-centred therapy requires physiological markers and appropriate disease definition. In the case of COPD for many years now, there have been discussions as to which COPD patients would benefit from “triple therapy” (LAMA/LABA/ICS). The recognized increased risk of pneumonia in certain COPD patients using ICS lead to attempts at better phenotyping patients. It is estimated in the current literature that about 25% to 30% of COPD patients benefit from the added ICS treatment. There is also research focused on trying to identify what defines the 25% to 30% of patients who benefits from LAMA/LABA/ICS. Whether a composite set of clinical features (e.g., history of asthma, normal diffusion capacity, minimal smoking history, etc.) or whether one specific marker (e.g., elevated peripheral eosinophils, sputum eosinophils, etc.) is the answer is still unclear, but research is focusing on this area because the cost associated with ICS in the treatment of COPD is high and because the complication (especially the rates of pneumonia) are significant and clinically relevant.

The new international and Canadian guidelines recommend bronchodilation and dual bronchodilation at the forefront of the therapeutic approach for COPD; bronchodilators are recommended as first-line treatment for symptomatic patients from GOLD, group A to D. Triple therapy (LAMA/LABA/ICS) is currently considered in patients with recurrent exacerbations despite dual bronchodilation. Even in this category of patients, adverse effects of corticosteroids should be monitored — especially patients developing radiologically proven pneumonia while on ICS should have their treatment approach reviewed.

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

A new concept in the management of COPD introduced in both GOLD 2017 and CTS 2017 is the concept of a "step-up" and "step-down" approach to management. A patient who is "stepped-up" to dual bronchodilation or on triple therapy in whom no improvement is noted (i.e., no change in symptoms or exercise tolerance, or exacerbation rate) could "step down" to the previous therapeutic regimen. The "step-down" concept allows all physicians to review patient "stability" and minimize pharmacological treatments.

Conclusions

Three phase III manufacturer-sponsored RCTs were included in this review, including two 24-week trials (FULFIL and Study 200812) and one 52-week trial (IMPACT). In the assessment of pulmonary function, treatment with FF/UMEC/VI showed statistically significant improvements in trough FEV_1 for comparisons with BUD/FOR at 24 weeks, FF/VI at 52 weeks, and UMEC/VI at 52 weeks. Clinical significance was achieved for the comparison with BUD/FOR at 24 weeks. Compared with its components, FF/UMEC/VI was noninferior based on a 0.050 L margin, where noninferiority was determined if the lower bound of the two-sided 95% CI around the treatment difference was above −0.050 L. Health-related quality of life was assessed via the SGRQ; improvements were identified for treatment with FF/UMEC/VI compared with BUD/FOR at 24 weeks, FF/VI at 52 weeks, and UMEC/VI at 52 weeks. FF/UMEC/VI was not statistically different from treatment with its components for changes in SGRQ. The annual rate of on-treatment moderate and severe exacerbations was improved for treatment with FF/UMEC/VI compared with treatment with BUD/FOR at 24 weeks, FF/VI at 52 weeks, and UMEC/VI at 52 weeks. FF/UMEC/VI was found to be not statistically different from treatment with its components on moderate or severe exacerbations. A manufacturer-provided NMA [redacted].

Adverse events were generally similar between FF/UMEC/VI and the other treatment arms in the three RCTs; however, the durations of the studies were potentially insufficient to draw clear inferences on the comparative rates of pneumonia and cardiovascular events. The reviewed NMA [redacted].

Table 1: Summary of Results

	FULFIL		IMPACT			Study 200812	
	FF/UMEC/VI 100/62.5/25 N = 911	BUD/FOR 400/12 N = 899	FF/UMEC/VI 100/62.5/25 N = 4,151	FF/VI 100/25 N = 4,134	UMEC/VI 62.5/25 N = 2,070	FF/UMEC/VI 100/62.5/25 N = 527	FF/VI + UMEC 100/25 + 62.5 N = 528
Pulmonary Function							
Baseline FEV_1 mean (SD)	1.28 (0.464)	1.27 (0.466)	1.17 (0.479)	1.17 (0.476)	1.17 (0.473)	1.15 (0.448)	1.19 (0.448)
n with analyzable data	836	781	3,366	3,060	1,490		
LS mean change from baseline trough FEV_1 (SE)	0.14 (0.008)[a]	−0.03 (0.008)[a]	0.094 (0.0042)	−0.003 (0.0044)	0.040 (0.0063)	0.113 (0.0112)	0.095 (0.0116)
Difference (95% CI)	0.17 (0.15 to 0.19)			0.097 (0.085 to 0.109)	0.054 (0.039 to 0.069)	0.018 (−0.013 to 0.050)[b]	
P value	< 0.001			< 0.001	< 0.001		
Moderate/Severe Exacerbations							
n	907	892	4,145	4,133	2,069		
Mean annual exacerbation rate	0.22	0.34	0.91	1.07	1.21		
Ratio (95% CI)	0.65 (0.49 to 0.86)[c]			0.85 (0.80 to 0.90)[d]	0.75 (0.70 to 0.81)[d]		
P value	0.002			< 0.001	< 0.001		
Time to first on-treatment moderate or severe exacerbation hazard ratio (95% CI)	0.67 (0.52 to 0.88)			0.85 (0.80 to 0.91)	0.84 (0.78 to 0.91)	0.87 (0.68 to 1.12)	
P value	0.004			<0.001	< 0.001		
SGRQ							
n with analyzable data	846	791	3,318	3,026	1,470		
Mean (SD)	51.8 (16.29)	50.8 (16.73)	45.0 (0.23)	46.8 (0.24)	46.8 (0.35)	49.0 (15.51)	48.5 (15.94)
LS mean change from baseline SGRQ Total Score[a] (SE)	−6.6 (0.45)	−4.3 (0.46)	−5.5 (0.23)	−3.7 (0.24)	−3.7 (0.35)	−5.84(0.59)[e]	−4.9 (0.59)[e]
Difference (95% CI)	−2.2 (−3.5 to −1.0)			−1.8 (−2.4 to −1.1)	−1.8 (−2.6 to −1.0)	−0.9 (−2.54 to 0.73)	
P value	< 0.001			< 0.001	< 0.001		

	FULFIL		IMPACT			Study 200812	
	FF/UMEC/VI 100/62.5/25 N = 911	BUD/FOR 400/12 N = 899	FF/UMEC/VI 100/62.5/25 N = 4,151	FF/VI 100/25 N = 4,134	UMEC/VI 62.5/25 N = 2,070	FF/UMEC/VI 100/62.5/25 N = 527	FF/VI + UMEC 100/25 + 62.5 N = 528
CAT							
Baseline CAT mean (SD)	17.6 (6.43)	17.8 (6.24)	18.2 (6.98)	18.3 (6.99)	18.1 (6.88)		
n with analyzable data	837	785	3,951	3,821	1,909		
LS mean change (SE)	−2.5 (0.18)	−1.6 (0.19)	−2.0 (0.11)	−1.5 (0.11)	−1.6 (0.16)		
Difference (95% CI)	−0.9 (−1.4 to −0.4)			−0.5 (−0.8 to −0.2)	−0.4 (−0.8 to −0.1)		
P value	< 0.001			< 0.001	0.021		
EXACT-RS							
Baseline mean (SD)	13.2 (5.83)	13.0 (5.93)	NA	NA	NA		
n	825	783	NA	NA	NA		
EXACT-RS treatment difference between weeks 21 to 24 (95% CI)	–1.35 (–1.79 to −0.91)		NA	NA	NA		
P value	< 0.001		NA	NA	NA		
Baseline Dyspnea Index Focal Score							
Mean (SD)	5.7 (1.77)	5.5 (1.83)	2,029	2014	1,015	6.4 (2.00)	6.33 (1.96)
Transition Dyspnea Index Focal Score			5.9 (1.94)	5.9 (1.98)	5.9 (1.99)		
n analysable data	839	788	1,549	1,861	670	482	481
LS Mean (SE)	2.29 (0.096)	1.72 (0.099)	0.98 (0.079)	0.71 (0.083)	0.89 (0.120)	2.029 (0.1252)	1.892 (0.1254)
Difference (95% CI)	0.57(0.30 to 0.84)			0.27 (0.04 to 0.49)	0.09 (–0.19 to 0.37)	0.137 (–0.211 to 0.485)	
P value	< 0.001			0.020	0.522	NA	
SAEs[†]							
N (%)	49 (5)	51 (6)	895 (22)	850 (21)	470 (23)	52 (10)	57 (11)
WDAEs							
N (%)	28 (3)	25 (3)	252 (6)	327 (8)	187 (9)	18 (3)	11 (2)
Deaths							
N (%)	4 (< 1)	6 (< 1)	68 (2)	76 (2)	49 (2)	4 (< 1)	4 (< 1)

	FULFIL		IMPACT			Study 200812	
	FF/UMEC/VI 100/62.5/25 N = 911	BUD/FOR 400/12 N = 899	FF/UMEC/VI 100/62.5/25 N = 4,151	FF/VI 100/25 N = 4,134	UMEC/VI 62.5/25 N = 2,070	FF/UMEC/VI 100/62.5/25 N = 527	FF/VI + UMEC 100/25 + 62.5 N = 528
Notable Harms, N (%)							
Anticholinergic syndrome	16 (1.8)	17 (1.9)	184 (4)	140 (3)	70 (3)	12 (2)	5 (< 1)
CV effects	39 (4.3)	47 (5.2)	450(11)	430 (10)	224 (11)	30 (6)	28 (5)
Local steroid effects	19 (2.1)	24 (2.7)	337 (8)	301 (7)	108 (5)	12 (2)	14 (3)
Pneumonia	20 (2.2)	7 (0.8)	317 (8)	292 (7)	97 (5)	14 (3)	21 (4)

BUD = budesonide; CAT = COPD Assessment Test; CI = confidence interval; CV = cardiovascular; EXACT-RS = EXAcerbations of Chronic Pulmonary Disease Tool – Respiratory Symptoms; FEV_1 = forced expiratory volume in 1 second; FF = fluticasone furoate; FOR = formoterol fumarate; LS = least squares; NA = not applicable; SAE = serious adverse event; SD = standard deviation; SE = standard error; SGRQ = St. George's Respiratory Questionnaire; UMEC = umeclidinium; VI = vilanterol; WDAE = withdrawal due to adverse event.

[a] Analysis performed using a repeated measures model with covariates of treatment group, smoking status (screening), geographical region, visit, baseline, and baseline-by-visit and treatment-by-visit interactions.

[b] Modified per-protocol population; NFF/UMEC/VI = 478, NFF/VI + UMEC = 478.

[c] Analysis performed using a generalized linear model assuming a negative binomial distribution and covariates of treatment group, exacerbation history (0, 1, ≥ 2 moderate/severe), smoking status (screening), geographical region, and post-bronchodilator per cent predicted FEV_1 (day 1).

[d] Analysis for the exacerbation rate was performed using a generalized linear model assuming a negative binomial distribution and covariates of treatment group, gender, exacerbation history (≤ 1, ≥ 2 moderate/severe), smoking status (Screening), geographical region, and post-bronchodilator per cent predicted FEV_1 (Screening).

[e] Analysis performed using a repeated measures model with covariates of baseline SGRQ, stratum (number of long-acting bronchodilators used during the run-in period: 0/1 or 2), visit number, geographical region, treatment, visit by treatment, and visit by baseline interaction.

[f] Frequency ≥ 1%.

Source: CSRs for FULFIL,[7] IMPACT,[8] Study 200812.[9]

Introduction

Disease Prevalence and Incidence

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable respiratory illness that includes chronic bronchitis and emphysema.[1,2] COPD is commonly caused by smoking; an estimated 80% to 90% of COPD cases are attributed to it.[1] COPD is caused by the complex interplay of a number of factors; these may include long-term cumulative exposure to occupational dusts and chemicals, second-hand smoke, frequent lung infections as a child, or exposure to wood smoke and other biomass fuel used for cooking, or for genetic reasons (alpha1-antitrypsin deficiency).[2,10] COPD is characterized by progressive, partially reversible airway obstruction and lung hyperinflation, systemic manifestations, and increasing frequency and severity of exacerbations.[1] It is also characterized by persistent inflammation of the airways lung parenchyma and its vasculature, resulting in limited expiratory flow. COPD is associated with several comorbidities including ischemic heart disease, osteopenia and osteoporosis, glaucoma and cataracts, cachexia and malnutrition, anemia, peripheral muscle dysfunction, cancer, and metabolic syndrome.[1]

COPD is an underdiagnosed illness; thus, prevalence statistics are likely to underestimate the number of people currently living with COPD. COPD has an estimated global prevalence of 7.6%.[11] In adults aged 40 and over, the global prevalence of COPD is between 9% and 10%.[11] The prevalence, morbidity, and mortality of COPD varies across the world.[10] In Canada, COPD is the fourth-leading cause of death[1]. According to a Statistics Canada report based on data from 2012 to 2015, it is estimated that 12% of Canadians aged 35- to 79-years-old have a measured airflow obstruction consistent with COPD.[3] Historically, COPD caused more deaths in men than women; however, in this report, there were no significant differences by sex.[3,12] New evidence suggests that women may be more susceptible to the effects of tobacco than men, possibly because of a difference in lung physiology, leading to more severe disease in women.[10] The prevalence of COPD increases with age.[1]

Patients with COPD are often limited in their day-to-day lives including their ability to breathe, talk, sleep, work, and socialize. Overall, patients describe a physically and mentally exhausting disorder that can result in anxiety, depression, and a decrease in quality of life. In addition, COPD has a profound effect on caregivers, who cite a number of challenges including limited time for managing their own health and well-being, feelings of depression and isolation, anxiety, stress, fatigue, a feeling of unending days, and increased requirements for social support.

The goals of COPD management are to prevent disease progression, reduce the frequency and severity of exacerbations, alleviate symptoms, improve exercise tolerance and daily activity, treat exacerbations and complications, improve health status, and reduce mortality.[4]

Standards of Therapy

Management decisions are guided by disease severity (i.e., symptoms and disability, and spirometry) and the frequency of acute exacerbations. Smoking cessation is the single most effective intervention to reduce the risk of developing COPD and the only intervention shown to slow the rate of lung function decline. [1,10] Regular exercise with cardiorespiratory conditioning can improve functional status and the sensation of dyspnea in COPD patients, more than the use of medications alone. Education and self-management skills are also an integral part of the non-pharmacological approach to the management of COPD. Pulmonary rehabilitation is recommended for all COPD patients who are symptomatic.

Bronchodilators form the mainstay of pharmacotherapy for COPD[5] and include long-acting beta-agonists (LABAs) such as salmeterol, formoterol, and indacaterol; or long-acting muscarinic antagonists (LAMA) such as tiotropium, glycopyrronium, aclidinium bromide, and umeclidinium. LAMAs and LABAs used in combination as a step-up therapy is recommended for patients with stable COPD with exacerbations despite the use of LAMA or LABA therapy.[5] As well, combinations of fixed-dose LABAs and inhaled corticosteroids (ICS) (or LABA + ICS), such as fluticasone/salmeterol, may be considered for certain patients with COPD; ICS are not recommended as monotherapy in COPD to prevent exacerbations and when used should only be combined with an inhaled LABA. Inhaled steroids may not be useful for mild disease; however, they may have more of a role in the management of moderate to severe COPD patients with two or more exacerbations (or one or more exacerbations leading to hospital admission) per year, or in those with persistent symptoms.[5,10,13-15] There may also be a subpopulation of COPD patients who have concomitant asthma or airway eosinophilia, where ICS use may be beneficial.[5,10,16-18] Patients with persistent symptoms and poor health status who continue to experience exacerbations despite inhaled LAMA/LABA dual therapy may be recommended to step-up to triple therapy composed of LAMA plus ICS/LABA.[5,10] Methylxanthines (such as theophylline) and phosphodiesterase inhibitors (roflumilast) are adjunctive therapies for COPD management that have a limited place in the treatment of COPD in Canada. Oxygen therapy is used in very severe COPD patients with persistent hypoxemia.

Drug

Trelegy Ellipta is the first triple combination therapy composed of an ICS (fluticasone furoate), a LABA (vilanterol), and a LAMA (umeclidinium).[6] Fluticasone furoate is a synthetic trifluorinated corticosteroid with potent, local anti-inflammatory activity, whereas the LABA and LAMA components act as long-acting bronchodilators via stimulation of the beta2 receptors and competitive inhibition of muscarinic receptors, respectively. This triple therapy is administered once daily as a dry powder for oral inhalation via the Ellipta inhaler. Each of the Trelegy Ellipta components is available in other formulations which also have Health Canada-approved indications for the management of COPD (Table 2). Fluticasone furoate/vilanterol (Breo Ellipta), umeclidinium/vilanterol (Anoro Ellipta), and umeclidinium (Incruse Ellipta) have received recommendations for reimbursement, with criteria and/or conditions, from the Canadian Drug Expert Committee for the management of COPD.

Table 2: Key Characteristics of Combination Drugs for Chronic Obstructive Pulmonary Disease

	Fluticasone Furoate/ Umeclidinium/ Vilanterol (Trelegy Ellipta)	Fluticasone Furoate/ Vilanterol (Breo Ellipta)	Budesonide/ Formoterol (Symbicort)	Fluticasone Propionate/ Salmeterol (Advair)	Umeclidi-nium/ Vilanterol (Anoro Ellipta)	Indacaterol/ Glycopyr-ronium (Utilbro)	Tiotropium/ olodaterol (Inspiolto Respimat)	Aclidinium Bromide/ Formoterol Fumarate (Duaklir)
Mechanism of Action	ICS: anti-inflammatory effects may treat the inflammation associated with COPD LABA: stimulation of beta2 receptors in the lungs leads to bronchodilation LAMA: competitive inhibition of muscarinic receptors	ICS: anti-inflammatory effects may treat the inflammation associated with COPD LABA: stimulation of beta2 in the lungs leads to bronchodilation	ICS: anti-inflammatory effects may treat the inflammation associated with COPD LABA: stimulation of beta2 receptors in the lungs leads to bronchodilation	ICS: anti-inflammatory effects may treat the inflammation associated with COPD LABA: stimulation of beta2 receptors in the lungs leads to bronchodilation	LAMA: competitive inhibition of muscarinic receptors LABA: stimulation of beta2 receptors in the lungs leads to bronchodilation	LAMA: competitive inhibition of muscarinic receptors LABA: stimulation of beta2 receptors in the lungs leads to bronchodilation	LAMA: competitive inhibition of muscarinic receptors LABA: stimulation of beta2 receptors in the lungs leads to bronchodilation	LAMA: competitive inhibition of muscarinic receptors LABA: stimulation of beta2 receptors in the lungs leads to bronchodilation
Indication[a]	COPD	COPD	COPD	COPD	COPD	COPD	COPD	COPD
Route of Adminis-tration	Inhalation	Inhalation	Inhalation	Inhalation	Inhalation	Inhalation	Inhalation	Inhalation
Recom-mended Dose	100/62.5/25 mcg once daily	100/25 mcg once daily	160/4.5 mcg twice daily	250/50 or 500/50 mcg twice daily	62.5/25 mcg once daily	110/50 mcg once daily	2.5/2.5 mcg once daily	400/12 mcg twice daily
Serious Side Effects/ Safety Issues	ICS component: • increased risk of pneumonia • immuno-suppression • adrenal suppression LABA component:	ICS component: • increased risk of pneumonia • immuno-suppression • adrenal suppression LABA component:	ICS component: • increased risk of pneumonia • immuno-suppression • adrenal suppression LABA	ICS component: • increased risk of pneumonia • immuno-suppression • adrenal suppression LABA	LAMA component: • increased risk of cardiovascular effects, ocular disorders, urinary retention,	LAMA component: • increased risk of cardiovascular effects, ocular disorders, urinary retention,	LAMA component: • increased risk of cardiovascular effects, ocular disorders, urinary retention,	LAMA component: • increased risk of cardiovascular effects, ocular disorders, urinary retention,

	Fluticasone Furoate/ Umeclidinium/ Vilanterol (Trelegy Ellipta)	Fluticasone Furoate/ Vilanterol (Breo Ellipta)	Budesonide/ Formoterol (Symbicort)	Fluticasone Propionate/ Salmeterol (Advair)	Umeclidi-nium/ Vilanterol (Anoro Ellipta)	Indacaterol/ Glycopyr-ronium (Utilbro)	Tiotropium/ olodaterol (Inspiolto Respimat)	Aclidinium Bromide/ Formoterol Fumarate (Duaklir)
	• increased risk of asthma-related death LAMA: • Increased risk of cardiovascular effects, ocular disorders, urinary retention, gastrointestinal disorders, dry mouth, and cough	• increased risk of asthma-related death	component: • Increased risk of asthma-related death	component: • Increased risk of asthma-related death	gastrointestinal disorders, dry mouth, and cough LABA: • Increased risk of asthma-related death	gastrointestinal disorders, dry mouth and cough. LABA component: • Increased risk of asthma-related death	gastrointestinal disorders, dry mouth, and cough. LABA component: • Increased risk of asthma-related death	gastrointestinal disorders, dry mouth, and cough. LABA component: • Increased risk of asthma-related death
Other	Delivery device: Ellipta	Delivery device: Ellipta	Delivery device: Turbuhaler	Delivery device: Diskus	Delivery device: Ellipta	Delivery device: Breezhaler	Delivery device: Respimat	Delivery device: Genuair

COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; LABA = long-acting beta2 agonist; LAMA = long-acting muscarinic antagonist; mcg = micrograms.

[a] Health Canada indication.

Source: Product Monograph for Trelegy Ellipta,[6] Breo Ellipta,[19] Anora Ellipta,[20] Symbicort,[21] Incruse Ellipta,[22] Advair,[23] Ultibro,[24] Inspiolto Respimat,[25] and Duaklir.[26]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta; 100/62.5/25 mcg) for the treatment of patients with COPD, including chronic bronchitis and/or emphysema, who have moderate to severe COPD; and are symptomatic and/or at risk of exacerbations despite the use of maintenance therapy with a LAMA, ICS/LABA, or LAMA/LABA; or currently on a LAMA/ICS/LABA.

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 and Health Canada, as well as those meeting the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient Population	Patients diagnosed with COPD, including chronic bronchitis and/or emphysema, who: have moderate to severe COPD; and are symptomatic and/or at risk of exacerbations despite use of maintenance therapy with a LAMA, ICS/LABA, or LAMA/LABA; or currently on a LAMA/ICS/LABA. Subgroups: • prior exacerbations • prior bronchodilator therapy • baseline disease severity • reversibility response rate • peripheral eosinophila	
Intervention	Fluticasone furoate 100 mcg/umeclidinium 52.5 mcg/vilanterol 25 mcg once daily, alone or in combination with conventional therapies	
Comparators	The following comparators were used in combination (as appropriate): • LABA • LAMA • ICS	
Outcomes	**Efficacy outcomes:** • mortality (all-cause) • mortality due to COPD • health care resource utilization (e.g., hospitalization, emergency room visits) • exacerbations,a and time to first exacerbation • health-related quality of lifea • lung function (e.g., spirometry, FEV1, expiratory capacity) • symptomsa (e.g., dyspneaa) • use of rescue medication	• exercise tolerancea • patient satisfaction/adherence • productivity[a] **Harms outcomes:** • SAEs • WDAE • AEs • AEs of special interest (e.g., CV, pneumonia, corticosteroid AE, anticholinergic AE)
Study Design	Published and unpublished phase III and IV RCTs	

AE=adverse event; COPD=chronic obstructive pulmonary disease; CV = cardiovascular; FEV_1=forced expiratory volume in one second; ICS=inhaled corticosteroids; LABA=long-acting beta2-agonists; LAMA = long-acting muscarinic antagonist; RCT=randomized controlled trial; SAE=serious adverse event; SC=subcutaneously; WDAE=withdrawal due to adverse events

[a] Outcome indicated as important from patient input.

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

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

Methodological filters were not applied to limit retrieval to any specify study designs. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on March 29, 2018. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on July 18, 2018. 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 (https://www.cadth.ca/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Databases, and an Internet search. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review 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 4; excluded studies (with reasons) are presented in Appendix 3.

Results

Findings From the Literature

A total of three studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

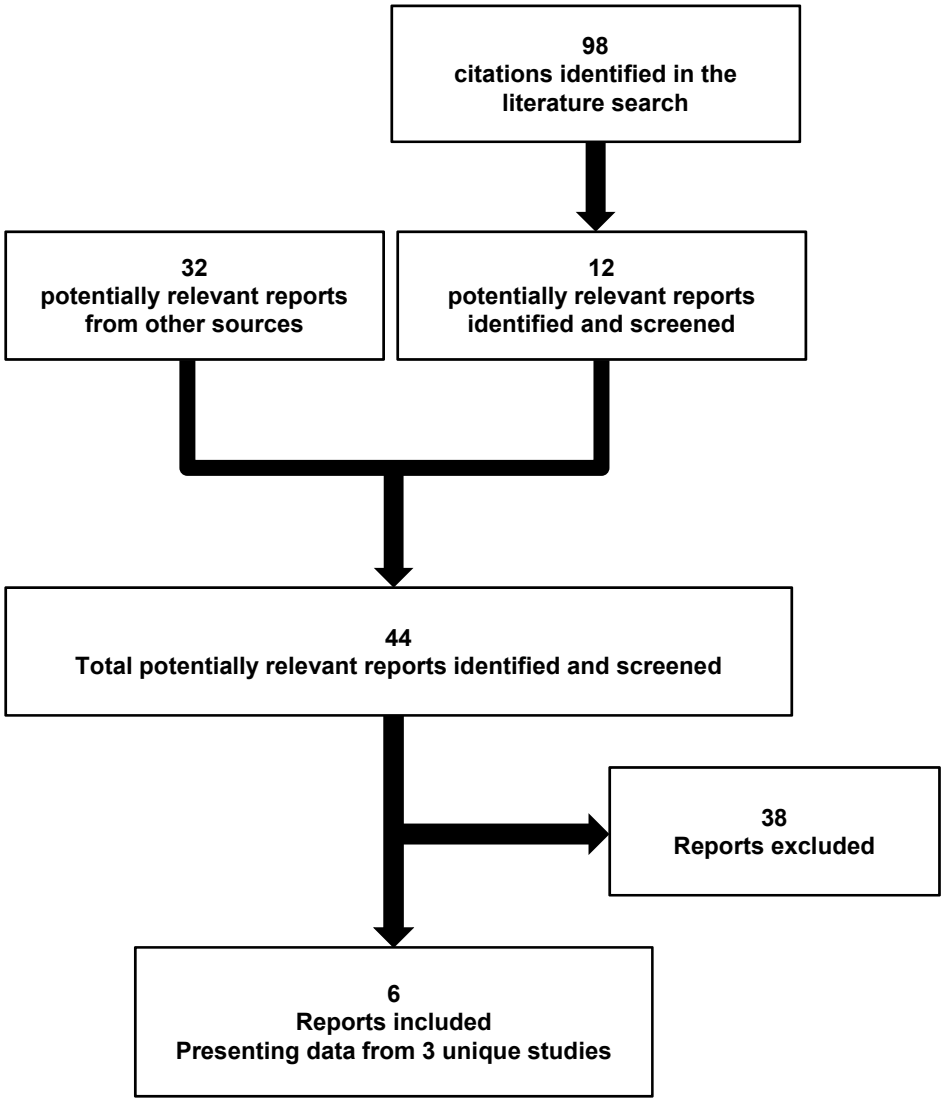


Table 4: Details of Included Studies

		FULFIL	IMPACT	Study 200812
Designs and Populations	**Study Design**	RCT, DB	RCT, DB	RCT, DB, noninferiority trial
	Locations	Europe, Asia, Central America	Western Europe, Asia, North America, South America	Europe, Asia, Australia, Argentina
	Randomized (N)	1,810	10,355	1,055
	Inclusion Criteria	Male and non-pregnant female patients ≥ 40 years of age who were current or former cigarette smokers (≥10 pack-years at screening) diagnosed with COPD as defined by the ATS/ERS. Score of ≥ 10 on the CAT, a post-bronchodilator FEV_1 < 50% predicted normal or a post-bronchodilator FEV_1 < 80% predicted normal and documented history of ≥ 2 moderate exacerbations or one severe (hospitalized) exacerbation in the previous 12 months, a post-salbutamol FEV_1/ FVC ratio of < 0.70	Male and non-pregnant female patients ≥ 40 years of age who were current or former cigarette smokers (≥10 pack-years at Screening) diagnosed with COPD as defined by the ATS/ERS. Score of ≥ 10 on the CAT, a post-bronchodilator FEV_1 < 50% predicted normal, and a documented history of ≥ 1 moderate or severe COPD exacerbation in the previous 12 months OR a post-bronchodilator 50% ≤ FEV_1 < 80% predicted normal and a documented history of ≥ 2 moderate exacerbations or a documented history of ≥ 1 severe (hospitalized) COPD exacerbation in the previous 12 months, a post-albuterol/salbutamol FEV_1/FVC ratio of < 0.70	Male and non-pregnant female patients ≥ 40 years of age who were current or former cigarette smokers (≥ 10 pack-years at screening) diagnosed with COPD as defined by the ATS/ERS. Score of ≥ 10 on the CAT, a post-bronchodilator FEV_1 < 50% predicted normal and a documented history of ≥ 1 moderate COPD exacerbation or ≥ 1 severe (hospitalized) exacerbation in the previous 12 months, or a post-bronchodilator 50% ≤ FEV_1 < 80% predicted normal and a documented history of ≥ 2 moderate exacerbations or a documented history of ≥ 1 severe (hospitalized) COPD exacerbation in the previous 12 months. A post-bronchodilator FEV_1/FVC ratio of < 0.70
	Exclusion Criteria	Current diagnosis of asthma, COPD caused by alpha-1-antitrypsin deficiency, other respiratory disorders, lung resection within 12 months of screening, or other clinically significant diseases (not including CV disease)	Current diagnosis of asthma, COPD caused by alpha-1-antitrypsin deficiency, other respiratory disorders, lung resection within 12 months of screening, or other clinically significant diseases (not including CV disease)	Current diagnosis of asthma, COPD caused by alpha-1-antitrypsin deficiency, other respiratory disorders, lung resection within 12 months of screening, or other clinically significant diseases (not including CV disease)
Drugs	**Intervention**	FF/UMEC/VI 100/62.5/25 mcg (via Ellipta) by inhalation q.d.	FF/UMEC/VI 100/62.5/25 mcg (via Ellipta) by inhalation q.d.	FF/UMEC/VI 100/62.5/25 mcg (via Ellipta) by inhalation q.d.
	Comparator(s)	BUD/FOR 400/12 mcg (via Turbuhaler) by inhalation q.d.	FF/VI 100/25 mcg (via Ellipta) by inhalation q.d. UMEC/VI 62.5/25 mcg (via Ellipta) by inhalation q.d.	FF/VI 100/25 mcg (via Ellipta) by inhalation q.d. plus UMEC 62.5 mcg (via Ellipta) by inhalation q.d.
Duration	**Phase**			
	Run-in	2 weeks	2 weeks	2 weeks
	Double-blind	24 weeks	52 weeks	24 weeks
	Follow-up	1 week	1 week	1 week

		FULFIL	IMPACT	Study 200812
Outcomes	**Primary End Point(s)**	Change from baseline in trough FEV_1 at week 24 Change from baseline in SGRQ total score at week 24	Annual rate of on-treatment moderate or severe exacerbations	Change from baseline in trough FEV_1 at week 24
	Other End Points[a]	Annual rate of on-treatment moderate or severe COPD exacerbations Assessment of respiratory symptoms using the EXACT-RS score TDI focal score at week 24	Change from baseline trough FEV_1 at week 52 Change from baseline SGRQ total score at week 52 Time to first on-treatment moderate or severe exacerbation TDI focal score at week 52 (subset[b])	Proportion of responders based on the SGRQ total score at week 24 Change from baseline in SGRQ total score at week 24 Proportion of responders based on TDI focal score at week 24 TDI focal score at week 24 Time to first moderate or severe COPD exacerbation
Notes	**Publications**	Lipson et al., 2017[27]	Lipson et al., 2018[28]	Bremner et al., 2018[29]

ATS = American Thoracic Society; BUD = budesonide; CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; DB = double-blind; ERS = European Respiratory Society; EXACT-RS = EXAcerbations of Chronic Pulmonary Disease Tool – Respiratory Symptoms; FEV_1 = forced expiratory volume in one second; FF = formoterol; fluticasone furoate; FOR = formoterol fumarate; FVC = forced vital capacity; q.d. = once daily; RCT = randomized controlled trial; SGRQ = St. George's Respiratory Questionnaire; TDI = Transitional Dyspnea Index; UMEC = umeclidinium; VI = vilanterol.

Note: Two additional reports were included (CDR submission[30] and Health Canada's reviewers report[31]).

[a] Included "other" end points are not an exhaustive list.

[b] Results for TDI available for subset of subjects at selected sites where translations were available (primarily in North American and Western Europe).

Source: CSRs for FULFIL,[7] IMPACT,[8] Study 200812.[9]

Included Studies

Description of Studies

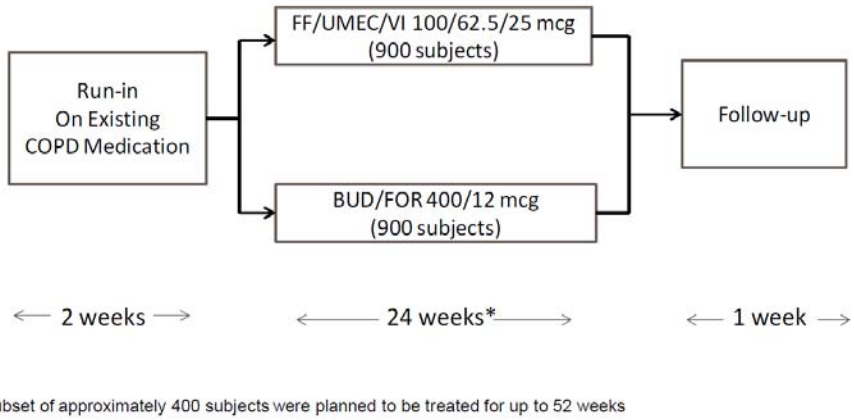
Five phase-three randomized controlled trials (RCTs) were identified by the manufacturer. These included two 12-week trials (Study 200109 and Study 200110), two 24-week trials (FULFIL and Study 200812) and one 52-week trial (IMPACT).[7-9,32,33] One pivotal trial was submitted (FULFIL) and two non-pivotal trials (200109 and 200110) were submitted to Health Canada's New Drug Submission. In a [redacted] an additional two pivotal trials were included (IMPACT and Study 200812). The focus of the formulary review is on the three pivotal trials (FULFIL, IMPACT, and Study 200812). The non-pivotal trials are described in Appendix 6.

FULFIL

FULFIL was a multi-national, 24-week, double-blind, double-dummy, manufacturer-sponsored randomized trial. The primary objective of FULFIL was to evaluate the effects of fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) on lung function and health-related quality of life (HRQL) compared with budesonide (BUD)/formoterol fumarate (FOR) after 24 weeks of treatment. Patients received training with the inhalation devices and eDiary (for recording device use, symptoms, etc.) at screening (day 1).The randomization

schedule for FULFIL was generated using GSK software (RANDALL Next Generation) on a site-specific basis, and patients were assigned to the study arms using the Registration and Medication Ordering System (RAMOS) — an Interactive Voice Response System. Patients were randomized in a 1:1 ratio for treatment with FF/UMEC/VI 100/62.5/25 mcg via the Ellipta once daily in the morning and placebo via the Turbuhaler twice daily, or treatment with BUD/FOR 400/12 mcg via the Turbuhaler twice daily and placebo via the Ellipta once daily in the morning. Randomization was stratified on smoking status (current smoker or former smoker). Patients underwent a run-in period of two weeks, where patients remained on their existing COPD medications and were provided with short-acting salbutamol for use as rescue medication. The run-in period was used to establish patients' use and compliance with the daily eDiary and baseline diary symptoms and salbutamol use. The continuous use of the patients' regular medication up to the initiation of the study drug was conducted to mimic switching scenarios seen in clinical practice.[27] Patients who failed the run-in period were not included in the main analysis population. Patients were enrolled from Europe, Asia, and Central America from approximately 200 sites. This study took place between January 23, 2015 and April 7, 2016. In the main study 1,810 patients were randomized, 911 patients were randomized to FF/UMEC/VI, and 900 patients were randomized to BUD/FOR. Patients enrolled in the trial were treated for 24 weeks and followed up for an additional week. A subset of 430 patients was included in an extension of the trial, where patients remained in the trial for a total of 52 weeks. These patients were the first to be enrolled in the main double-blind randomized controlled phase and who consented to also be included in the extension; details of this extension group are described in Appendix 7. Figure 2 shows a visual representation of the study design for FULFIL.

Figure 2: Design of FULFIL



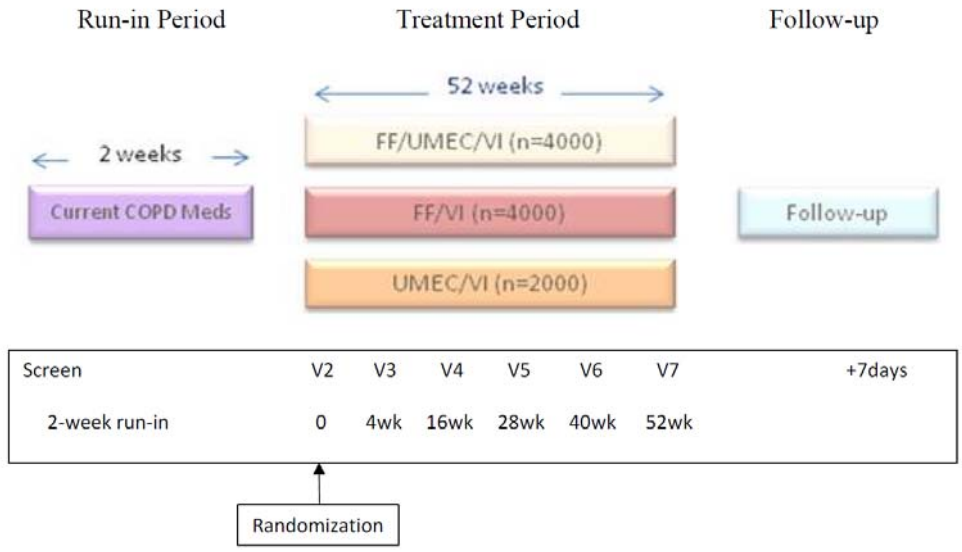
BUD = budesonide; COPD = chronic obstructive pulmonary disease; FF = fluticasone furoate; FOR = formoterol; UMEC = umeclidinium; VI = vilanterol.
Source: CSR for FULFIL.[7]

IMPACT

IMPACT was a multi-national, 52-week, double-blind, parallel-group, manufacturer-sponsored randomized trial. The primary objective of IMPACT was to evaluate the efficacy of FF/UMEC/VI to reduce the annual rate of moderate/severe exacerbations compared with dual therapy of FF/VI or UMEC/VI in patients with COPD. Patients received training with the inhalation devices and eDiary (for recording device use, symptoms, etc.) at screening (day 1). The randomization schedule for IMPACT was generated using GSK software

(RANDALL Next Generation) on a site-specific basis, and patients were assigned to study arms using the RAMOS in a 2:2:1 ratio for once daily treatment via the Ellipta with FF/UMEC/VI 100/62.5/25 mcg, FF/VI 100/25 mcg, or UMEC/VI 62.5/25 mcg, respectively. Randomization was not stratified. Patients underwent a run-in period of two weeks where patients remained on their existing COPD medications and were provided salbutamol for use as rescue medication. Patients were enrolled from Western Europe, Asia, North America, South America from approximately 1,200 sites. This study was took place between June 30, 2014 and July 17, 2017. In IMPACT 10,355 patients were randomized; 4,155 patients were randomized to FF/UMEC/VI, 4,139 patients were randomized to FF/VI, and 2,073 patients were randomized to UMEC/VI. Patients enrolled in the trial were treated for 52 weeks and followed up for an additional week. Figure 3 shows a visual representation of the study design for IMPACT.

Figure 3: Design of IMPACT



COPD = chronic obstructive pulmonary disease; FF = fluticasone furoate; UMEC = umeclidinium; V = visit; VI = vilanterol, wk = week.

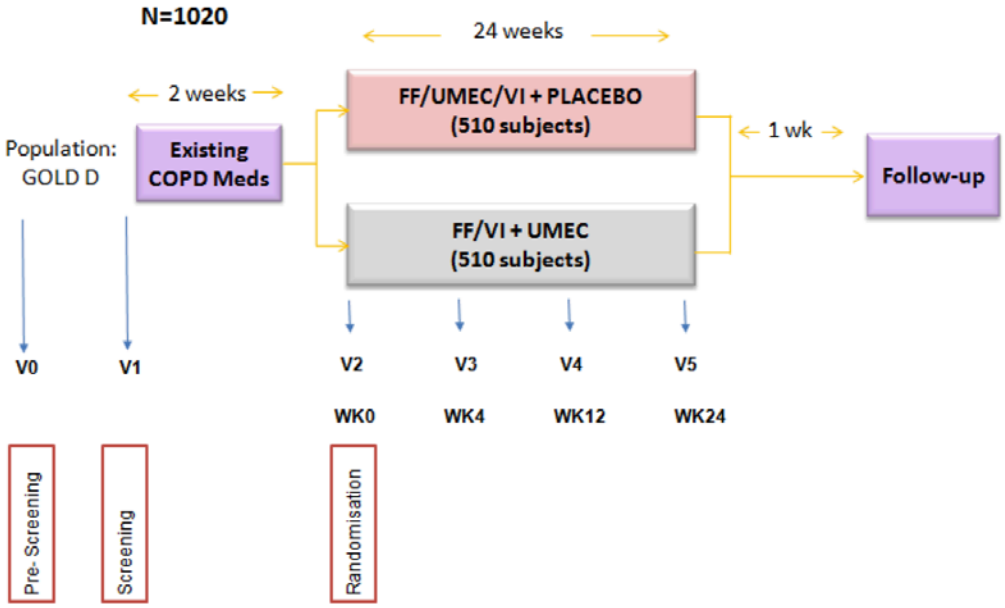
Source: CSRs for IMPACT.[8]

Study 200812

Study 200812 was a multi-national, 24-week, double-blind, parallel-group, manufacturer-sponsored randomized trial. This noninferiority trial aimed to compare the effect of FF/UMEC/VI with FF/VI+UMEC on lung function after 24 weeks of treatment. The change from baseline in trough forced expiry volume in one second (FEV_1) was assessed using a noninferiority margin of 0.050 L (approximately one-half the estimated minimal clinically important difference [MCID]). Patients received training on the use of an electronic device (for recording responses to questionnaires) at screening (day 1). The randomization schedule for Study 200812 was generated using GSK software (RANDALL Next Generation) on a country-specific basis, and patients were assigned to study arms in a 1:1 ratio for treatment with FF/UMEC/VI 100/62.5/25 mcg via the Ellipta once daily in the morning and placebo via the Ellipta once daily in the morning, or treatment with FF/VI 100/25 mcg via the Ellipta once daily in the morning and UMEC 62.5 mcg via the Ellipta once daily in the morning. Randomization was stratified on long-acting bronchodilator

(e.g., LABA or LAMA) use during the run-in period (none, one or two long-acting bronchodilators per day). Patients who were classified as pre-screen failures were assigned a participant number but did not attend the screening visit. Patients underwent a run-in period of two weeks, where patients remained on their existing COPD medications and were provided with salbutamol for use as rescue medication. Patients were enrolled from Europe, Asia, and Argentina from approximately 126 sites. This study took place between June 29, 2016 and May 23, 2017. In Study 200812, 1,055 patients were randomized; 537 patients were randomized to FF/UMEC/VI and 528 patients were randomized to FF/VI + UMEC. Patients enrolled in the trial were treated for 24 weeks and followed up for an additional week. Figure 4 shows a visual representation of the study design for Study 200812.

Figure 4: Design of Study 2000812



COPD = chronic obstructive pulmonary disease; FF = fluticasone furoate; GOLD = Global initiative for chronic Obstructive Lung Disease; Meds = medications; UMEC = umeclidinium; V = visit; VI = vilanterol; wk = week.

Source: CSRs for Study 200812.[9]

Populations

Inclusion and Exclusion Criteria

The study populations for FULFIL, IMPACT, and Study 200812 consisted of patients 40 years of age and older. Across trials, most of the inclusion criteria were identical. All trials included patients who were former or current smokers, had a diagnosis of COPD using the American Thoracic Society / European Respiratory Society definition, and a post-salbutamol FEV_1/ forced vital capacity (FVC) ratio of less than 0.70. Patients were also required to have a score of 10 or more on the COPD Assessment Test (CAT). The CAT assesses the impact of COPD on a patient's health status; a score of 10 or more indicates medium, high (> 20 points), or very high (> 30 points) impact.[34] The trials differed in the criteria related to FEV_1 and exacerbation history. FULFIL required either a post-bronchodilator FEV_1 of less than 50% predicted normal, or a post-bronchodilator FEV_1 of

less than 80% predicted normal and a documented history of two or more moderate exacerbations or one severe (hospitalized) exacerbation in the previous year. In contrast, both IMPACT and Study 200812 required either a post-bronchodilator FEV_1 of less than 50% predicted normal and a documented history of one or more moderate or severe COPD exacerbation in the previous 12 months, or a post-bronchodilator FEV_1 of ≥ to 50% and less than 80% of the predicted normal and a documented history of two or more moderate exacerbations or a documented history of one or more severe (hospitalized) COPD exacerbations in the previous year. Exclusion criteria across the three studies were: patients with a diagnosis of asthma, COPD associated with an alpha-1-antitrypsin deficiency, other respiratory disorders, lung resection within 12 months of screening, or other clinically significant diseases. Patients with cardiovascular disease were not excluded from the trials.

Baseline Characteristics

The baseline characteristics were relatively balanced between arms for each study. Across studies, males contributed to 66% to 75% of patients within treatment arms, the mean (standard deviation) age of patients ranged from 63.7 (8.71) to 66.7 (8.46) years, and the percentage of patients classified as current smokers ranged from 34% to 44%.

The majority of patients had moderate (32% to 37%) or severe (47% to 55%) COPD using the GOLD grade; 14% to 20% of patients were classified as reversible, where they demonstrated an increase in FEV_1 of 12% or more, and 200 mL or more following the administration of salbutamol. Table 5 summarizes the baseline characteristics for each trial.

Table 5: Summary of Baseline Characteristics

	FULFIL		IMPACT			Study 200812	
	FF/UMEC/VI 100/62.5/25 N = 911	BUD/FOR 400/12 N = 899	FF/UMEC/VI 100/62.5/25 N = 4151	FF/VI 100/25 N = 4134	UMEC/VI 62.5/25 N = 2070	FF/UMEC/VI 100/62.5/25 N = 527	FF/VI + UMEC 100/25 + 62.5 N = 528
Male, n (%)	678 (74)	663 (74)	2,766 (67)	2,748 (66)	1,356 (66)	391 (74)	394 (75)
Age, years Mean (SD)	64.2 (8.56)	63.7 (8.71)	65.3 (8.24)	65.3 (8.30)	65.2 (8.26)	66.7 (8.46)	65.9 (8.77)
Ethnicity, n (%)							
Not Hispanic / not Latino	817 (90)	804 (89)	3,490 (84)	3,471 (84)	1,732 (84)	456 (87)	451 (85)
Hispanic/Latino	94 (10)	95 (11)	661 (16)	662 (16)	338 (16)	71 (13)	77 (15)
Smoking status, n (%)							
Current smoker	400 (44)	394 (44)	1,436 (35)	1,423 (34)	728 (35)	209 (40)	192 (36)
Former smoker	511 (56)	505 (56)	2,715 (65)	2,711 (66)	1,342 (65)	318 (60)	336 (64)
GOLD Grade, n (%)							
1 (mild)	0	1 (< 1)	10 (< 1)	8 (< 1)	4 (< 1)	0	1 (< 1)
2 (moderate)	298 (33)	291 (32)	1,535 (37)	1,455 (35)	729 (35)	174 (34)	189 (37)
3 (severe)	503 (55)	480 (54)	1,934 (47)	2,031 (49)	1,017 (49)	251 (49)	253 (49)
4 (very severe)	107 (12)	125 (14)	666 (16)	639 (15)	319 (15)	90 (17)	69 (13)
Post-bronchodilator FEV_1/FVC ratio							
Mean (SD)	0.45 (0.108)	0.45 (0.108)	0.47 (0.119)	0.47 (0.119)	0.47 (0.122)	0.44 (0.116)	0.45 (0.119)
Exacerbation History[a]							
< 2 moderate and no severe	418 (46)	421 (47)	1,198 (29)	1,242 (30)	616 (30)	175 (33)	168 (32)
≥ 2 moderate or ≥ 1 severe	493 (54)	478 (53)	2,953 (71)	2,892 (70)	1,454 (70)	352 (67)	360 (68)

	FULFIL		IMPACT			Study 200812	
	FF/UMEC/VI 100/62.5/25 N = 911	BUD/FOR 400/12 N = 899	FF/UMEC/VI 100/62.5/25 N = 4151	FF/VI 100/25 N = 4134	UMEC/VI 62.5/25 N = 2070	FF/UMEC/VI 100/62.5/25 N = 527	FF/VI + UMEC 100/25 + 62.5 N = 528
CAT Score, Mean (SD)	19.2 (5.23)	19.1 (5.21)	20.1 (6.10)	20.1 (6.13)	[redacted]	[redacted]	[redacted]
Reversible,[b] n (%)							
Yes	132 (15)	154 (17)	734 (18)	810 (20)	366 (18)	73 (14)	74 (14)
COPD medications taken at screening,[c] n (%)							
ICS + LABA	268 (29)	259 (29)	1,103 (27)	1,067 (26)	523 (25)	144 (27)	137 (26)
ICS + LABA + LAMA	257 (28)	256 (28)	1,396 (34)	1,433 (35)	734 (35)	198 (38)	193 (37)
LABA + LAMA	101 (11)	84 (9)	330 (8)	308 (7)	163 (8)	62 (12)	76 (14)
LAMA	79 (9)	79 (9)	273 (7)	331 (8)	140 (7)	32 (6)	35 (7)
LABA	37 (4)	42 (5)	98 (2)	105 (3)	42 (2)	NA	NA
ICS + LABA + LAMA + Xanthine	33 (4)	44 (5)	142 (3)	88 (2)	67 (3)	29 (6)	25 (5)
ICS + LABA + Xanthine	19 (2)	18 (2)	109 (3)	103 (2)	51 (2)	NA	NA
ICS	15 (2)	12 (1)	109 (3)	109 (3)	55 (3)	NA	NA
LABA + LAMA + Xanthine	10 (1)	12 (1)	NA	NA	NA	NA	NA
ICS + LAMA	5 (< 1)	11 (1)	42 (1)	36 (< 1)	18 (< 1)	NA	NA
LAMA + Xanthine	NA	NA	NA	NA	NA	NA	NA
ICS + LABA + LAMA + PDE4 inhibitors	NA	NA	39 (< 1)	41 (< 1)	21 (1)	NA	NA

BUD = budesonide; CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; FEV_1 = forced expiratory volume in one second; FF = formoterol; fluticasone furoate; FOR = formoterol fumarate; FVC = forced vital capacity; GOLD = Global initiative for chronic Obstructive Lung Disease; LABA = long-acting beta2-agonist; LAMA = long-acting muscarinic antagonist; PDE4 = phosphodiesterase type 4 inhibitor; SD = standard deviation; UMEC = umeclidinium; VL = vilanterol.

[a] Moderate or severe exacerbations in the past year. Moderate exacerbation: required treatment with oral/systemic corticosteroids and/or antibiotics (not involving hospitalization). Severe exacerbation: required hospitalization.

[b] Reversible is an increase in FEV_1 of ≥ 12% and ≥ 200 mL following administration of salbutamol.

Source: CSRs for FULFIL,[7] IMPACT,[8] Study 200812.[9]

Interventions

In FULFIL, patients received treatment with FF/UMEC/VI 100/62.5/25 mcg via the Ellipta once daily in the morning and placebo via the Turbuhaler twice daily, or treatment with BUD/FOR 400/12 mcg via the Turbuhaler twice daily and placebo via the Ellipta once daily in the morning. FULFIL was 24 weeks in duration. Patients received training with the inhalation devices and eDiary (for recording device use, symptoms, etc.) at screening (day 1).

In IMPACT, patients received once daily treatment with FF/UMEC/VI 100/62.5/25 mcg, FF/VI 100/25 mcg, or UMEC/VI 62.5/25 mcg. IMPACT was 52 weeks in duration. Patients received training with the inhalation devices and eDiary (for recording device use, symptoms etc.) at screening (day 1).

In Study 200812, patients received treatment with FF/UMEC/VI 100/62.5/25 mcg via the Ellipta once daily in the morning and placebo via the Ellipta once daily in the morning, or treatment with FF/VI 100/25 mcg via the Ellipta once daily in the morning and UMEC 62.5 mcg via the Ellipta once daily in the morning. Patients received training on the use of an electronic device (for recording responses to questionnaires) at screening (day 1).

Across all trials, patients were permitted the use of salbutamol for use as rescue medications. Medications including oral or injectable corticosteroids, antibiotics, and any other COPD medication (medically necessary for short-term treatment of an exacerbation or pneumonia) could be used for the treatment of exacerbations or pneumonia for a period not exceeding 14 days. Mucolytics, long-term oxygen therapy, and maintenance phase of pulmonary rehabilitation treatment were permitted. All COPD medications (except for rescue salbutamol, mucolytics, and oxygen) were prohibited during the study except for the treatment of a moderate or severe exacerbation or pneumonia.

Outcomes

The change from baseline in trough FEV_1 was evaluated as a co-primary outcome (at week 24) in FULFIL, the primary outcome (at week 24) in Study 200812, and as a secondary outcome (at week 52) in IMPACT. Trough FEV_1 was obtained from the largest of three acceptable spirometry efforts before the morning dose of the intervention and after withholding albuterol/salbutamol for four or more hours, if applicable. FEV_1 is the volume of air that, after a full inspiration, can be forcibly expired in one second. Trough FEV_1 is recognized as a component of the GOLD classification of airflow limitation severity in COPD.[10] The generally accepted clinically important change in FEV_1 is between 0.10 L and 0.14 L.[35]

The change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score (at week 24) was evaluated as a co-primary outcome in FULFIL, an “other” outcome (at week 52) in IMPACT, and a secondary outcome (at week 24) in Study 200812. In each trial, the SGRQ for COPD patients (SGRQ-C) was used, then scores were converted to the SGRQ. Scores on the SGRQ range from 0 to 100. A higher score on the SGRQ indicates a poorer level of health-related quality of life and decreases in score are indicative of improvement in health-related quality of life. A decrease of four points from baseline is considered a clinically meaningful improvement.[36]The annual rate of on-treatment moderate or severe exacerbations was evaluated as a primary outcome in IMPACT and a secondary outcome in FULFIL (not assessed in Study 200812). Potential exacerbations were identified by symptoms reported by patients in an eDiary, followed by confirmation from the investigator. A moderate exacerbation was defined as requiring treatment with oral/systemic corticosteroids and/or antibiotics (not involving hospitalization). A severe exacerbation required in-patient hospitalization. If necessary, the patient’s study treatment could be suspended in order to treat the COPD exacerbation.

The Transition Dyspnea Index (TDI) focal score was evaluated as a secondary outcome in FULFIL and Study 200812, and an “other” outcome in IMPACT. TDI measures changes in dyspnea severity from the baseline, as established by the Baseline Dyspnea Index (BDI). The TDI consists of 24 items, which are graded; lower scores indicate more deterioration related to an increase in the severity of dyspnea from baseline. The TDI focal score is composed of three different scales for functional impairment, magnitude of task, and magnitude of effort. The TDI focal score is calculated as the sum of the three individual scores and then divided by two. The range of the TDI focal score is −9 to +9. [37,38] A change in one point is considered clinically meaningful.[37]

The CAT was evaluated as a secondary outcome across trials. The CAT consists of eight items that address the following: cough, phlegm, chest tightness, breathlessness going up a hill or stairs, activity limitation at home, confidence in leaving home, sleep, and energy. Each item is scored from zero to five units, with a total scale score ranging from zero to 40 units, where higher scores represent worse health.[34] The reported MCID for the CAT

was two to four units.[39,40] The CAT authors suggest that a total score of < 10 units relates to low impact on health status, 10 to 20 units as medium impact, 21 to 30 units as high impact, and 30 to 40 units as very high impact.

FULFIL evaluated the EXAcerbations of Chronic Pulmonary Disease Tool – Respiratory Symptoms (EXACT-RS) as a secondary outcome. The EXACT-RS is composed of 11 or the 14 items from the EXACT. The EXACT-RS has a score that ranges from zero to 40, with higher scores indicating more severe symptoms. Evidence based from a single study estimated the MCID of 3.35 for the EXACT-RS.

A number of harms outcomes were reported including the following: adverse events, severe adverse events, withdrawals due to adverse events, and mortality. Notable harms were reported for anticholinergic syndrome, cardiovascular effects, and pneumonia.

Statistical Analysis

The change from baseline in trough FEV_1 was evaluated as a co-primary outcome (at week 24) in FULFIL, the primary outcome (at week 24) in Study 200812, and as a secondary outcome (at week 52) in IMPACT. The change from baseline in SGRQ total score (at week 24) was evaluated as a co-primary outcome in FULFIL, an "other" outcome (at week 52) in IMPACT, and a secondary outcome (at week 24) in Study 200812. The annual rate of on-treatment moderate/severe exacerbations was evaluated as a primary outcome in IMPACT and a secondary outcome in FULFIL.

A number of secondary or other end points were included in the trials. Relevant to this review, secondary end points included the following:

- time to first moderate or severe COPD exacerbation
- TDI focal score at week 24
- assessment of respiratory symptoms using the EXACT-RS score.

FULFIL

In FULFIL, the sample size was based on the co-primary efficacy end points (trough FEV_1 and SGRQ total score). An estimated 900 patients per arm were required to achieve 90% power to detect a difference of 2.5 units between FF/UMEC/VI and BUD/FOR assuming a standard deviation of 12 units for SGRQ total score and to achieve more than 90% power to detect an 80 mL difference in trough FEV_1 assuming a standard deviation of 240 mL. The power calculation was performed for a two-sided significance of 0.01. This sample size accounts for a 30% withdrawal. Assumptions were based on internal data, as well as studies by Wedzicha et al.,[41] Donohue et al.,[42] and Bateman et al.[43]

FULFIL had the following two co-primary efficacy end points assessed at week 24: the change from baseline in trough FEV_1, and the change from baseline in SGRQ total score. The co-primary end points were assessed using a mixed model repeated measures (MMRM) analysis using two-sided hypothesis testing. For theses analyses, the derived treatment differences were adjusted via modelling of the within-participant correlation structure to account for missing data. The following covariates were accounted for: treatment group, smoking status (screening), geographical region, visit, baseline value, and baseline-by-visit and treatment group-by-visit interactions. For these end points, the least squares (LS) means and LS mean change from baseline values for each treatment group, with associated standard errors and 95% confidence intervals (CI), were calculated, along with *P* values that were unadjusted and adjusted for multiplicity.

For the co-primary end points, the Hochberg method was used to account for multiplicity, thereby controlling type I error at alpha = 0.05. The statistical tests were performed at the 5% significance level. If the largest unadjusted *P* value for the two comparisons was greater than 0.05, then the other comparison would be declared statistically significant if the smaller unadjusted *P* value was less than 0.025. Missing data for patients who discontinued the study treatment was not accounted for in the main analysis (modified intention to treat [ITT]) but was explored in a sensitivity analysis. Patients who discontinued treatment were not required to withdraw from the study; if they did not withdraw consent, they could continue in the study to provide off-treatment data.

Several secondary end points were evaluated in FULFIL, including the annual rate of on-treatment moderate and severe exacerbations, the TDI focal score, and the EXACT-RS. None of the analyses for secondary end points were adjusted for multiplicity. The annual rate of on-treatment moderate or severe exacerbations was analyzed using a generalized linear model assuming a negative binomial distribution and adjusting for the following covariates: treatment group, exacerbation history, smoking status (screening), geographical region, and post-bronchodilator per cent-predicted FEV_1 at baseline, with logarithm of time on-treatment as an offset variable. The TDI focal score and EXACT-RS were analyzed using MMRM analysis.

IMPACT

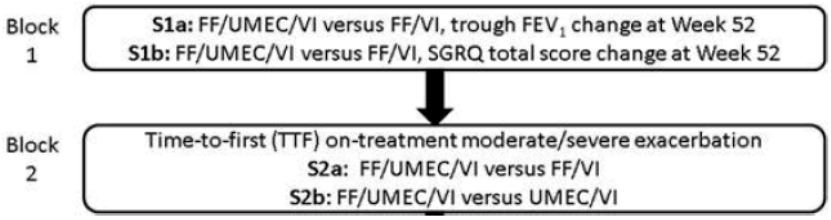
In IMPACT, the sample size was based on the co-primary treatment comparisons for the rate of on-treatment moderate or severe exacerbations for comparisons of FF/UMEC/VI with FF/VI, and FF/UMEC/VI with UMEC/VI. An estimated 4,000 patients were required for the FF/UMEC/VI and FF/VI arms, along with 2,000 patients for the UMEC/VI arm to achieve 90% power [redacted].

The annual rate of on-treatment moderate and severe exacerbations was evaluated as the primary end point in IMPACT. The co-primary treatment comparisons were assessed using a generalized linear model assuming a negative binomial distribution accounting for the following covariates: treatment group, gender, exacerbation history, smoking status (Screening), geographical region, and post-bronchodilator per cent-predicted FEV_1 (Screening). The model-estimated exacerbation rates and associated 95% CIs and pairwise treatment rate ratios were presented. To control for multiplicity for the comparisons between the two arms, the Hochberg method was used, thereby controlling type I error at alpha = 0.05. This method allowed for both comparisons to be statistically significant if the unadjusted *P* value for both comparisons was less than 0.04; and if one comparison had a *P* value greater than 0.04, the other comparison would be statistically significant if the smaller unadjusted *P* value was below 0.025. [redacted]

Secondary end points included the change from baseline in trough FEV_1 and SGRQ at 52 weeks, and time to first on-treatment moderate or severe COPD exacerbation. The TDI focal score was assessed as an “other” outcome. The change from baseline in trough FEV_1 and SGRQ were assessed using MMRM analysis; LS means and LS mean change with 95% CIs were reported. Time to first on-treatment of moderate to severe COPD exacerbation

was assessed using the Cox proportional hazards model; hazard ratios and 95% CIs were presented. Multiplicity was controlled using a hierarchical, closed testing procedure where secondary hypothesis tests were grouped in two blocks depicted in Figure 5. Blocks 1 and 2 were adjusted for multiplicity using the same procedure as the primary analysis. At least one end point must have been statistically significant in the previous block to be able to make inferences in the subsequent block. That is, statistical significance must have been satisfied for at least one outcome comparison in the primary outcome analysis before the end points in Block 1 could be compared. Likewise, for inferences to be drawn on comparisons in Block 2, at least one of the outcomes in Block 1 would need to be statistically significant. Subsequent statistical comparisons were not adjusted for multiplicity.

Figure 5: Secondary Efficacy End Point Hierarchy for IMPACT



Source: IMPACT Reporting and Analysis Plan.[44]

Study 200812

In Study 200812, the sample size was based on the primary efficacy end point for the change from baseline in trough FEV_1 at week 24, when the margin of noninferiority was 0.050 L and the true mean treatment difference was assumed to be 0 mL using a one-sided 2.5% significance level. The noninferiority margin of 0.050 L was selected based on the manufacturer's claim of it being half of the generally accepted MCID for the change in trough FEV_1 (0.10 L). An estimated 1,020 patients were required to achieve 90% power, taking into account a 20% withdrawal. The estimated residual standard deviation of 0.220 L was based on a mixed model repeated measures analyses of previous phase IIIa studies in patients with COPD.

The primary efficacy end point (the change from baseline in trough FEV_1 at week 24) was analyzed using an MMRM analysis modelled using the following covariates: baseline FEV_1, stratum (number of long-acting bronchodilators used during the run-in period), visit number, geographical region, treatment, visit by baseline interaction, and visit by treatment interaction. [redacted] Noninferiority was determined if the lower bound of the two-sided 95% CI around the treatment difference was above −0.050 L. [redacted]

Secondary outcomes, the change in SGRQ total score from baseline, and the TDI focal score were analyzed using an MMRM analysis with no imputation. Covariates included baseline SGRQ score/BDI, stratum (number of long-acting bronchodilators used during the run-in period: 0/1 or 2), visit number, geographical region, treatment, visit by baseline/BDI interaction, and visit by treatment interaction. The time to first moderate or severe COPD

exacerbation was analyzed using the Cox proportional hazards model. Covariates included treatment group, gender, exacerbation history, stratum, geographical region, and baseline FEV_1. [redacted]

Analysis Populations

FULFIL, IMPACT, and Study 200812 included the following two analysis populations:

- the all-patients-enrolled population that included all patients who signed a consent form and had records in the study database regardless of being screened or not
- the ITT population that included all randomized patients (excluding those randomized in error).

FULFIL included the following five additional analysis populations:

- the extension population that included all patients in the ITT population enrolled into the subset of patients (approximately 400) with extension to 52 weeks.

IMPACT included the following additional analysis population:

- the TDI population that included patients in the ITT population who completed a pre-dose BDI assessment at day 1.

Study 200812 included the following additional analysis population:

- the modified per-protocol population that included patients in the ITT population who did not have a full protocol deviation considered to impact efficacy (known as the adherent population).

Patient Disposition

The proportion of patients who discontinued each trial was balanced between trial arms. IMPACT had the highest proportion, where 11% to 14% of patients discontinued compared with 5% to 6% seen in the other trials; this is expected, as IMPACT was 52 weeks in duration and the other trials were 24 weeks. Study discontinuation was most often attributed to withdrawal of consent (1% to 6% across trial arms).

Table 6: Patient Disposition

	FULFIL		IMPACT			Study 200812	
	FF/UMEC/VI 100/62.5/25	BUD/FOR 400/12	FF/UMEC/VI 100/62.5/25	FF/VI 100/25	UMEC/VI 62.5/25	FF/UMEC/VI 100/62.5/25	FF/VI + UMEC 100/25 + 62.5
Enrolled/ Pre-Screened, N	2,121		[redacted]			1,311	
Pre-Screen Failure, N	59		[redacted]			33	
Screened, N	2,062		[redacted]			1,278	
Screen Failure, N	252		[redacted]			175	
Randomized, N	911	900	[redacted]	[redacted]	[redacted]	537	528
Discontinued Study, N (%)	45 (5)	57 (6)	[redacted]	[redacted]	[redacted]	30 (6)	32 (6)
Adverse event	16 (2)	19 (2)	[redacted]	[redacted]	[redacted]	21 (4)	11 (2)
Study closed/terminated	NA	NA	[redacted]	[redacted]	[redacted]	NA	NA

	FULFIL		IMPACT			Study 200812	
	FF/UMEC/VI 100/62.5/25	BUD/FOR 400/12	FF/UMEC/VI 100/62.5/25	FF/VI 100/25	UMEC/VI 62.5/25	FF/UMEC/VI 100/62.5/25	FF/VI + UMEC 100/25 + 62.5
Lost to follow-up	0	1 (< 1)	[redacted]	[redacted]	[redacted]	1 (< 1)	2 (< 1)
Investigator discretion	4 (< 1)	4 (< 1)	[redacted]	[redacted]	[redacted]	1 (< 1)	1 (< 1)
Withdrew consent	25 (3)	33 (4)	[redacted]	[redacted]	[redacted]	6 (1)	17 (3)
Subject relocated	NA	NA	[redacted]	[redacted]	[redacted]	NA	NA
Frequency of visits	NA	NA	[redacted]	[redacted]	[redacted]	NA	NA
Burden of procedures	NA	NA	[redacted]	[redacted]	[redacted]	NA	NA
Other	NA	NA	[redacted]	[redacted]	[redacted]	NA	NA
Unknown	NA	NA	[redacted]	[redacted]	[redacted]	NA	NA
ITT,[a] N	911	899	[redacted]	[redacted]	[redacted]	527	528
Extension, N	210	220	NA	NA	NA	NA	NA
mPP, N	NA	NA	NA	NA	NA	478	478

BUD = budesonide; FF = fluticasone furoate; FOR = formoterol fumarate; mPP = modified per protocol; ITT = intention to treat; UMEC = umeclidinium; VI = vilanterol.

[a] ITT population based on trial-specific definition of "ITT."

Source: CSRs for FULFIL,[7] IMPACT,[8] Study 200812.[9]

Exposure to Study Treatments

In FULFIL, the mean duration of treatment exposure was similar between treatment arms (163.2 days for FF/UMEC/VI and 158.2 days for BUD/FOR), with more than 90% of patients exposed to treatment for 20 or more weeks in both arms. The mean treatment compliance was higher for patients in the FF/UMEC/VI arm (99.8%) compared with the BUD/FOR arm (96.8%). Compliance with study treatment was assessed at each clinic visit using the Ellipta dry powder inhaler dose counter, which displays the number of doses remaining. Patients who were non-compliant received further instruction on the importance of treatment compliance.

In IMPACT, the mean duration of treatment exposure was higher in the FF/UMEC/VI arm [redacted] compared with the FF/VI arm [redacted] and the UMEC/VI arm [redacted]. In the FF/UMEC/VI, FF/VI, and UMEC/VI arms, [redacted] and [redacted] of patients were exposed to treatment for 51 to 53 weeks, respectively. The overall mean treatment compliance was similar between arms ranging from [redacted].

In Study 200812, the mean duration of treatment exposure was similar between treatment arms (162.1 days for FF/UMEC/VI and 162.1 days for FF/VI+UMEC), with more than 90% of patients exposed to treatment for 23 to 25 weeks in both arms. The overall mean treatment compliance was similar between arms, ranging from 98.3% to 98.8%.

Exposure to other COPD medications used during the trial was balanced between trial arms across all trials.

Critical Appraisal

Internal Validity

FULFIL, IMPACT, and Study 200812 were randomized, double-blind, parallel-group trials. Each trial was clearly described with specific objectives, end points, and interventions. The trials clearly described the randomization component in sequence generation. The randomization schedule for these trials was generated using GSK software (RANDALL Next Generation) by site for FULFIL and IMPACT, and by country for Study 200812. For FULFIL and IMPACT, treatments were assigned using an interactive voice response system. For Study 200812, the method of randomization was not reported. In FULFIL, randomization was stratified based on smoking status, and in Study 200812, randomization was stratified on long-acting bronchodilator use during the run-in (none, one, or two long-acting bronchodilators per day). The baseline demographics and disease characteristics were similar between treatment arms in each trial, suggesting successful randomization.

In each study, both the patients and investigators were blinded. Measures were taken to ensure blinding throughout the studies. In FULFIL, study treatments were delivered using different inhalers (Ellipta and Turbuhaler); to ensure blinding, placebo inhalers that matched in appearance were used to maintain blinding. In IMPACT and Study 200812, all medications were administered via Ellipta. In Study 200812, a placebo via Ellipta was administered in the FF/UMEC/VI group, as the comparison treatment arm required therapy to be administered via two separate Ellipta inhalers, thereby enhancing study blinding.

The patient disposition for each trial was clearly presented. IMPACT had a higher proportion of patients who discontinued the trial compared with FULFIL and Study 200812; this is likely because of the 52-week length of IMPACT compared with the 24-week length of the other trials. In all trials, the proportion of patients who discontinued the trial was balanced between trial arms.

The primary outcomes assessed in the trials related to trough FEV_1, SGRQ, and the annual rate of on-treatment moderate and severe exacerbations. The FEV_1 is used in clinics and recommended by GOLD to grade the airflow limitation severity in patients with COPD.[10] The generally accepted clinically important change in FEV_1 is between 0.10 L and 0.14 L. Study 200812 was a noninferiority trial that assessed the difference in least squares change from baseline in trough FEV_1 at 24 weeks for FF/UMEC/VI compared with FF/VI + UMEC. Noninferiority was assessed using a margin of 0.050 L (approximately one-half the MCID for change in trough FEV_1). The use of this margin was confirmed to be clinically relevant by the clinical expert consulted for this review. This outcome was assessed in a modified per-protocol analysis and a population described as ITT; however, it should be noted that this was not a true ITT population, as imputation was not performed. Both analysis sets showed noninferiority as the lower bound of the two-sided 95% CI around the treatment difference was above −0.050 L.

The SGRQ is a disease-specific measure of HRQL that was specifically developed for patients with airways obstruction. The SGRQ-C is a COPD-specific version composed of fewer items but designed to produce scores that are equivalent to the SGRQ, using an algorithm.[45] This subscale consists of 40 of the 50 questions in the SGRQ. In each trial, the SGRQ-C score was converted to a SGRQ score, which was subsequently used to assess patients. Whereas the SGRQ-C was used in each of the trials, it was reported as the SGRQ; the rationale for this was unclear. A decrease of four points is considered a

clinically meaningful improvement in the SGRQ and, by extension, in the SGRQ-C. In FULFIL, a responder based on SGRQ was defined as an SGRQ total score of four or more units below baseline; this definition coincides with the MCID, suggesting it is an appropriate threshold.

The assessment of exacerbations was based on moderate exacerbation (defined as requiring treatment with oral/systemic corticosteroids and/or antibiotics [not involving hospitalization]) and severe exacerbations (defined as requiring in-patient hospitalization).

In FULFIL, multiplicity was controlled in the assessment of the co-primary efficacy end points (change from baseline in trough FEV_1 and SGRQ total score). All assessments for all other end points were not controlled for multiplicity. This lack of control for multiplicity increases the likelihood of reporting false-positive reports (increased type I error) and creates issues with interpreting results. FULFIL based its main analysis on an ITT population composed of all individuals randomized. FULFIL did not use imputation in this analysis, thus this was not a true ITT population. Missing data were not accounted for in the primary analyses but was explored in sensitivity analyses that included data from patients who discontinued the study treatment.

In IMPACT, multiplicity was controlled in the assessment of the co-primary treatment comparisons (for the rate of on-treatment moderate and severe exacerbations for comparisons of FF/UMEC/VI with FF/VI and FF/UMEC/VI with UMEC/VI). Only a few of the secondary outcomes were controlled for multiplicity using a hierarchical, closed testing procedure using two blocks. A rationale was not provided for why only a few of the secondary outcomes were controlled for multiplicity. Block 1 was restricted to analyses of comparisons between UMEC/FF/VI and FF/VI, while block 2 included analyses versus FF/VI and versus UMEC/VI. Missing data were not accounted for in the primary analysis but was explored in sensitivity analyses using the jump to reference imputation method for the co-primary efficacy end points.

In Study 200812, none of the treatment comparisons for secondary outcomes were controlled for multiplicity. Missing data were not accounted for in any of the analyses except in a “tipping point” sensitivity analysis for the primary efficacy end point, using multiple imputation.

The patient disposition for each trial was clearly presented. In all trials, the proportion of patients who discontinued the trial was balanced between trial arms.

External Validity

In FULFIL, IMPACT, and Study 200812, patients were recruited globally. Although IMPACT was the only trial that included Canadians, the clinical expert expected the results of each trial to be generalizable to the Canadian population with COPD. Baseline demographics and disease characteristics were generally consistent with what would be seen in the Canadian population with COPD; however, the overrepresentation of male patients was noted. FULFIL required either a post-bronchodilator FEV_1 of less than 50% predicted normal, or a post-bronchodilator FEV_1 of less than 80% predicted normal and a documented history of two or more moderate exacerbations or one severe (hospitalized) exacerbation in the previous year. In contrast, both IMPACT and Study 200812 required either a post-bronchodilator FEV_1 of less than 50% predicted normal and a documented history of one or more moderate or severe COPD exacerbations in the previous 12 months, or a post-bronchodilator FEV_1 of greater than or equal to 50% and less than 80% of the

predicted normal, and a documented history of two or more moderate exacerbations or a documented history of one or more severe (hospitalized) COPD exacerbations in the previous year. The clinical expert noted that this difference would not create a clinically relevant difference, as all trials had the same inclusion requirements for the post-salbutamol FEV_1/FVC ratio (less than 0.70). The three trials were designed to be inclusive of patients with COPD by not excluding patients with cardiovascular disease from entry into the trials.

The comparators and doses used in the trials were deemed to be clinically relevant and appropriate by the clinical expert; however, it was noted that comparisons with other dual bronchodilators besides UMEC/VI would have been of interest. The use of comparators administered via Ellipta were especially relevant, as the consistency in device and particle size reduced the potential for device-related differences. In FULFIL, the comparator BUD/FOR 400/12 mcg was administered via Turbuhaler; this difference in device was unavoidable because of current availability.

The main outcomes measures (CAT, EXACT-RS, FEV_1, and SGRQ) were all considered to be valid outcome measures for patients with COPD. In patient input, it was determined that outcomes pertaining to exacerbations, health-related quality of life, and symptoms (i.e., dyspnea) were of interest; these coincide with the outcomes that were assessed in the trials. The duration of the trials was expected to be sufficient in order to assess the most of the efficacy and harms outcomes, as two trials were 24 weeks in duration (FULFIL and Study 200812) and one trial (IMPACT) was 52 weeks in duration. It is likely that 24 weeks was likely insufficient to assess the long-term effects of corticosteroids and occurrence of exacerbations.

Across trials, patients were excluded if they had a current diagnosis of asthma. It was unlikely that the diagnosis of asthma was confirmed via spirometry, as patients in each study were classified as reversible at baseline, where following the administration of salbutamol there was an increase in FEV_1 of 12% or more and 200 mL or more. The proportion of patients with reversibility were balanced between trial arms, so their inclusion would not create a differential impact on the efficacy results. While COPD and asthma are distinct diseases, the Canadian Thoracic Society (CTS) has reported on the growing recognition that many patients with COPD present with features of asthma (referred to as the Asthma-COPD overlap [ACO]). In 2017, the CTS created the following definition of ACO: “ACO is characterized by post-bronchodilator airflow limitation that is not fully reversible, in symptomatic patients with risk factors for COPD and who have clinical features of both asthma and COPD.”[5] The CTS has proposed three diagnostic criteria and two treatment recommendations. The classification of ACO based on the CTS-supported definition is novel and yet to be used as a differentiating class in clinical trials.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported here (Table 3). Studies selected for inclusion in the systematic review included the pivotal studies provided in the manufacturer’s submission to CDR, as well as those meeting the selection criteria presented in Table 3. See Appendix 4 for detailed efficacy data.

Pulmonary Function

In FULFIL, the change from baseline in trough FEV_1 at 24 weeks for FF/UMEC/VI compared with BUD/FOR was 0.17 L (95% CI, 0.15 L to 0.19 L). The improvement in FEV_1 was statistically significant ($P < 0.001$) and clinically significant (MCID = 0.10 L to 0.14 L)

(Table 7). The within-group improvement in FEV_1 was clinically significant for FF/UMEC/VI. A sensitivity analysis where data from patients who discontinued the study treatment was included produced similar results to the primary analysis, where improvements with FF/UMEC/VI were seen compared with BUD/FOR.

In IMPACT, the change from baseline in trough FEV_1 at 52 weeks for FF/UMEC/VI compared with FF/VI was 0.097 L (95% CI, 0.085 L to 0.109 L), and compared with UMEC/VI was 0.054 L (95% CI, 0.039 L to 0.069 L). The improvement in FEV_1 was statistically significant ($P < 0.001$) but not clinically significant (MCID = 0.10 L to 0.14 L) for FF/UMEC/VI compared with both FF/VI and UMEC/VI (Table 8). The within-group improvement in FEV_1 was not clinically significant for FF/UMEC/VI.

In Study 200812, the change from baseline in trough FEV_1 at 24 weeks for FF/UMEC/VI compared with FF/VI + UMEC, was 0.018 L (95% CI, −0.013 L to 0.050 L) for the modified per-protocol (adherent) population, and 0.026 L (95% CI, −0.002 L to 0.053 L) in the ITT population. The improvement in FEV_1 for FF/UMEC/VI compared with FF/VI + UMEC/VI was noninferior, as the lower bound of the two-sided 95% CI around the treatment difference was above −0.050 L (Table 9). A "tipping point" sensitivity analysis was conducted to explore the impact of missing data (using multiple imputation) by using differing assumptions regarding the mean treatment effect. It was determined that the conclusion of noninferiority no longer holds when FF/UMEC/VI has an LS mean of 150 mL or more worsening change compared with FF/VI+UMEC in change from baseline in trough FEV_1.

Exacerbations

In FULFIL, the annualized rate of on-treatment moderate or severe exacerbations during the 24-month study was lower in the FF/UMEC/VI arm than in the BUD/FOR arm (0.22 versus 0.34, respectively), with a rate ratio of 0.65 (95% CI, 0.49 to 0.86, $P = 0.002$). The ratio for time to first on-treatment for moderate or severe exacerbation showed a reduction for FF/UMEC/VI compared with BUD at week 24 (hazard ratio [HR] = 0.67, 95% CI 0.52 to 0.88, $P = 0.004$) (Table 7).

In IMPACT, the annualized rate of on-treatment moderate or severe exacerbations during the 52-month study was lower in the FF/UMEC/VI arm than in both the FF/VI and UMEC/VI arms (0.91 versus 1.07 and 1.21, respectively); these differences were statistically significant ($P < 0.001$), with rate ratios of 0.85 (95% CI, 0.80 to 0.90) and 0.75 (95% CI, 0.70 to 0.81) for comparisons with FF/VI and UMEC/VI, respectively. A sensitivity analysis where the data from patients who discontinued the study treatment was included produced similar results to the primary analysis, where improvements with FF/UMEC/VI were seen compared with FF/VI, and UMEC/VI. The ratio for time to first on-treatment moderate or severe exacerbation showed significant reductions for FF/UMEC/VI compared with FF/VI and UMEC/VI at week 52 (HR = 0.85, 95% CI, 0.80 to 0.91, $P < 0.001$ for FF/VI, and HR = 0.84, 95% CI, 0.78 to 0.91, $P < 0.001$ for UMEC/VI) (Table 8).

In Study 200812, the ratio for time to first on-treatment moderate or severe exacerbation for FF/UMEC/VI compared with FF/VI + UMEC showed no statistical difference (HR = 0.87, 95% CI, 0.68 to 1.12) (Table 9).

Health-Related Quality of Life

HRQL was assessed using the SGRQ and the EuroQuol 5-Dimensions 5-Levels questionnaire (EQ-5D-5L). The change from baseline in SGRQ total score was evaluated as a co-primary outcome in FULFIL, an "other" outcome (at week 52) in IMPACT, and a

secondary outcome (at week 24) in Study 200812. The EQ-5D-5L was assessed in FULFIL and IMPACT as part of a health outcomes analysis. This outcome was assessed descriptively with no between-group statistical comparisons performed (Appendix 4, Table 13).

In FULFIL, the change from baseline in SGRQ total score at 24 weeks for FF/UMEC/VI compared with BUD/FOR was −2.2 units (95% CI, −3.5 units to −1.0 units). The improvement in SGRQ was statistically significant at 24 weeks ($P < 0.001$) but not clinically significant (MCID = 4 units) (Table 7). The within-group improvement in SGRQ was clinically significant for FF/UMEC/VI. A sensitivity analysis for where data from patients who discontinued the study treatment was included produced similar results to the primary analysis, where improvements with FF/UMEC/VI were seen compared with BUD/FOR.

In IMPACT, the change from baseline in SGRQ total score at 52 weeks for FF/UMEC/VI compared with FF/VI was −1.8 units (95% CI, −2.4 units to −1.1 units, and compared with UMEC/VI was −1.8 units (95% CI, −2.6 units to −1.0 units); these differences were statistically significant ($P < 0.001$) but not clinically significant (MCID = 4 units) (Table 8). The within-group improvement in SGRQ was clinically significant for FF/UMEC/VI.

In Study 200812, the change from baseline in SGRQ total score at 24 weeks for FF/UMEC/VI compared with FF/VI + UMEC showed no statistical difference (–0.906 units, 95% CI, −2.540 units to 0.728 units) (Table 9).

Other Efficacy Outcomes

FULFIL evaluated COPD-related respiratory symptoms using the EXACT-RS. Greater reductions from baseline in the EXACT-RS were found at four-week intervals over 24 weeks. The treatment difference between week 21 and 24 was −1.35 units (95% CI, −1.79 units to −0.91 units, $P < 0.001$) (Table 7). Clinical significance was unclear, as this outcome was not adjusted for multiplicity and no excepted MCID value was found in the literature.

All trials assessed the severity of dyspnea using the TDI focal score. In FULFIL, the difference in LS mean TDI focal score showed improvement in FF/UMEC/VI compared with BUD/FOR at 24 weeks (0.57 units, 95% CI, 0.30 units to 0.84 units, $P < 0.001$) (Table 7). In IMPACT, the difference in LS mean TDI focal score showed improvement in FF/UMEC/VI compared with FF/VI at 52 weeks [redacted] but not for UMEC/VI at 52 weeks [redacted] (Table 8). In Study 200812, the difference in LS mean TDI focal score showed no statistical difference between FF/UMEC/VI and FF/VI + UMEC at 24 weeks (0.137 units, 95% CI, −0.211 units to 0.485 units) (Table 9).

FULFIL and IMPACT assessed the health status and disease impact using the CAT. In FULFIL, the difference in LS mean change was determined to show improvement for FF/UMEC/VI compared with BUD/FOR at 24 weeks (−0.9 units, 95% CI, −1.4 to −0.4, $P < 0.001$) (Table 7). In IMPACT, the difference in LS mean change was determined to show improvement for FF/UMEC/VI compared with FF/VI at 52 weeks [redacted] and for UMEC/VI at 52 weeks [redacted] (Table 8).

FULFIL and IMPACT assessed the use of rescue medications. In FULFIL, a statistically significant reduction in the mean number of occasions of rescue medication use compared with BUD/FOR was determined at 24 weeks (–0.2 occasions, 95% CI, −0.3 occasions to

−0.1 occasions, *P* < 0.001)(Table 7). In IMPACT, a reduction in the mean number of occasions of rescue medication use compared with both FF/VI and UMEC/VI was determined at 52 weeks [redacted] (Table 8).

Subgroup Outcomes

Efficacy outcomes by the eosinophil subgroup (less than 150 cells/μL, ≥150 cells/μL) were reported in IMPACT and presented in Appendix 4, Table 12). The change from baseline trough FEV_1 showed improvements for FF/UMEC/VI compared with both FF/VI and UMEC/VI in both subgroups. The annual model-estimated exacerbation rate showed improvements for FF/UMEC/VI compared with both FF/VI and UMEC/VI in both subgroups. The time to first on-treatment moderate or severe exacerbation [redacted]. The difference in TDI [redacted].

Table 7: Efficacy Outcomes for FULFIL

	Modified ITT Population (24 Weeks)	
	FF/UMEC/VI 100/62.5/25 N = 911	BUD/FOR 400/12 N = 899
Pulmonary Function		
Baseline FEV_1 mean (SD)	1.28 (0.464)	1.27 (0.466)
n with analyzable data at week 24	836	781
LS mean change from baseline trough FEV_1[a] (SE)	0.14 (0.008)	−0.03 (0.008)
Difference (95% CI)	0.17 (0.15 to 0.19)	
Adjusted *P* value[b]	< 0.001	
Moderate/Severe Exacerbations		
n	907	892
Mean annual exacerbation rate[c]	0.22	0.34
Ratio (95% CI)	0.65 (0.49 to 0.86)	
P value	0.002	
Time to first on-treatment moderate or severe exacerbation hazard ratio (95% CI)	0.67 (0.52 to 0.88)	
P value	0.004	
SGRQ		
n with analyzable data at week 24	846	791
Mean (SD)	51.8 (16.29)	50.8 (16.73)
LS mean change from baseline SGRQ total score[a] (SE)	−6.6 (0.45)	−4.3 (0.46)
Difference (95% CI)	−2.2 (−3.5 to −1.0)	
Adjusted *P* value[b]	< 0.001	
P value	< 0.001	
SGRQ responder[d], N (%)	448 (50)	368 (41)
CAT		
Baseline CAT mean (SD)	17.6 (6.43)	17.8 (6.24)
n with analyzable data at week 24	837	785
LS mean change (SE)	−2.5 (0.18)	−1.6 (0.19)

	Modified ITT Population (24 Weeks)	
	FF/UMEC/VI 100/62.5/25 N = 911	BUD/FOR 400/12 N = 899
Difference (95% CI)	−0.9 (−1.4 to −0.4)	
P value	< 0.001	
EXACT-RS		
Baseline mean (SD)	13.2 (5.83)	13.0 (5.93)
n	825	783
EXACT-RS treatment difference between weeks 21 to 24 (95% CI)	−1.35 (−1.79 to −0.91)	
P value	< 0.001	
Baseline Dyspnea Index Focal Score		
Mean (SD)	5.7 (1.77)	5.5 (1.83)
Transition Dyspnea Index Focal Score		
n analysable data at week 24	839	788
LS mean (SE)	2.29 (0.096)	1.72 (0.099)
Difference (95% CI)	0.57(0.30 to 0.84)	
P value	< 0.001	
Rescue Medication		
Baseline mean use per day (SD)	1.8 (2.07)	1.8 (2.04)
n	870	859
LS mean change (SE)	−0.1 (0.04)	0.1 (0.04)
Difference (95% CI)	−0.2 (−0.3 to −0.1)	
P value	< 0.001	

BUD = budesonide; CAT = COPD assessment test; CI = confidence interval; EXACT-RS = EXAcerbations of Chronic Pulmonary Disease Tool – Respiratory Symptoms; FEV_1 = forced expiratory volume in one second; FF = fluticasone furoate; FOR = formoterol fumarate; ITT = intention to treat; LS = least squares; SD = standard deviation; SE = standard error; SGRQ = St. George's Respiratory Questionnaire; UMEC = umeclidinium; VI = vilanterol.

Note: Multiplicity controlled for co-primary end points (change from baseline in trough FEV_1 and SGRQ total score).

[a] Analysis performed using a repeated measures model with covariates of treatment group, smoking status (screening), geographical region, visit, baseline, and baseline-by-visit and treatment-by-visit interactions.

[b] Adjusted for multiplicity. The adjusted *P* value at week 24 was compared against a reference level of 0.05 in order to infer statistical significance.

[c] Analysis performed using a generalized linear model assuming a negative binomial distribution and covariates of treatment group, exacerbation history (0, 1, ≥ 2 moderate/severe), smoking status (screening), geographical region, and post-bronchodilator per cent-predicted FEV_1 (day 1).

[d] Response was defined as an SGRQ Total Score of ≥ 4 units below baseline. Non-response was defined as an SGRQ total score of < 4 units below baseline or data missing for the analysis.

Source: CSR for FULFIL.[7]

Table 8: Efficacy Outcomes for IMPACT

	IMPACT		
	FF/UMEC/VI 100/62.5/25 N = 4,151	FF/VI 100/25 N = 4,134	UMEC/VI 62.5/25 N = 2,070
Pulmonary Function			
Baseline FEV_1 Mean (SD)	[redacted]	[redacted]	[redacted]
N with analyzable data at week 52	3,366	3,060	1,490
LS mean change from baseline trough FEV_1 (SE)	0.094 (0.0042)	–0.003 (0.0044)	0.040 (0.0063)
Difference (95% CI)		0.097 (0.085 to 0.109)	0.054 (0.039 to 0.069)
Unadjusted *P* value		< 0.001	< 0.001
Adjusted *P* value[a]		< 0.001	–
Moderate or Severe Exacerbations			
N (Annual model-estimated exacerbation rate)	4,145	4,133	2,069
Annual model-estimated exacerbation rate[b]	0.91	1.07	1.21
Rate ratio (95% CI)		0.85 (0.80 to 0.90)	0.75 (0.70 to 0.81)
Adjusted *P* value[c]		< 0.001	< 0.001
N (Time to first on-treatment moderate or severe exacerbation)	[redacted]	[redacted]	[redacted]
Time to first on-treatment moderate or severe exacerbation hazard ratio (95% CI)[d]		0.85 (0.80 to 0.91)	0.84 (0.78 to 0.91)
Adjusted *P* value		< 0.001	< 0.001
Mortality			
Risk of on-treatment all-cause mortality, hazard ratio (95% CI)		0.95 (0.64 to 1.40)	0.58 (0.38 to 0.88)
P value		0.780	0.011
SGRQ			
N with analyzable data at week 52	3,318	3,026	1,470
LS mean (SE)	45.0 (0.23)	46.8 (0.24)	46.8 (0.35)
LS mean change from baseline SGRQ total score (SE)	–5.5 (0.23)	–3.7 (0.24)	–3.7 (0.35)
Difference (95% CI)		–1.8 (–2.4 to −1.1)	–1.8 (–2.6 to −1.0)
Unadjusted *P* value		< 0.001	< 0.001
Adjusted *P* value[a]		< 0.001	–
SGRQ responders (%)[e]	1,723 (42)	1,390 (34)	696 (34)
CAT			
Baseline CAT mean (SD)	[redacted]	[redacted]	[redacted]
N with analyzable data at week 52	3,951	3,821	1,909
LS mean change (SE)	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]
P value		[redacted]	[redacted]
Rescue Medication[f]			
Baseline mean use per day (SD)	[redacted]	[redacted]	[redacted]
N with analyzable data at week 52	[redacted]	[redacted]	[redacted]
LS mean change (SE)	[redacted]	[redacted]	[redacted]

	IMPACT		
	FF/UMEC/VI 100/62.5/25 N = 4,151	FF/VI 100/25 N = 4,134	UMEC/VI 62.5/25 N = 2,070
Difference (95% CI)		[redacted]	[redacted]
P value		[redacted]	[redacted]
Baseline Dyspnea Index Focal Score			
N	2,029	2014	1,015
Mean (SD)	[redacted]	[redacted]	[redacted]
Transition Dyspnea Index Focal Score[G]			
N with analyzable data at week 52	1,549	1,861	670
LS mean (SE)	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]
P value		[redacted]	[redacted]

CAT = COPD assessment test; CI = confidence interval; FEV_1 = forced expiratory volume in one second; FF = fluticasone furoate; LS = least squares; SD = standard deviation; SE = standard error; SGRQ = St. George's Respiratory Questionnaire; UMEC = umeclidinium; VI = vilanterol.

Note: Multiplicity controlled for co-primary end points (for the rate of on-treatment moderate/severe exacerbations for comparisons of FF/UMEC/VI with FF/VI and FF/UMEC/VI with UMEC/VI) and some secondary end points described in the statistical analysis section.

[a] The unadjusted and adjusted *P* value at week 52 should be compared against a reference level of 0.05 in order to infer statistical significance for the comparisons of FF/UMEC/VI versus FF/VI.

[b] Analysis for the exacerbation rate was performed using a generalized linear model assuming a negative binomial distribution and covariates of treatment group, gender, exacerbation history (≤ 1, ≥ 2 moderate/severe), smoking status (Screening), geographical region, and post-bronchodilator per cent predicted FEV_1 (Screening).

[c] The adjusted *P* values should be compared against a reference level of 0.05 in order to infer statistical significance for either of the comparisons.

[d] Response was defined as an SGRQ Total Score of four units below baseline or lower. Non-response was defined as an SGRQ Total Score higher than 4 units below baseline or a missing SGRQ Total Score with no subsequent non-missing on-treatment scores. Subjects did not have a responder status derived if baseline SGRQ Total Score was missing. Subjects did not have a responder status derived at particular visits where the SGRQ Total Score was missing but subsequent on-treatment SGRQ Total Scores were present. Analysis was performed using a generalized linear mixed model with a logit link function and covariates of treatment group, smoking status (Screening), geographical region, visit, baseline, baseline-by-visit, and treatment group-by-visit interactions.

[e] Hazard ratio and 95% CI were from a Cox proportional hazards model with covariates of treatment group, gender, exacerbation history (≤ 1, ≥ 2 moderate/severe), smoking status (Screening), geographical region, and post-bronchodilator per cent predicted FEV_1 (Screening).

[f] Analysis was performed using a repeated measures model with covariates of treatment group, smoking status (Screening), geographical region, four-weekly time period, baseline, and baseline-by-four-weekly time period and treatment-group-by-four-weekly time period interactions.

[g] The Transition Dyspnea Index Population included 5,058 patients at selected sites who completed a pre-dose Baseline Dyspnea Index assessment at day 1.

Source: CSR for IMPACT.[8]

Table 9: Key Efficacy Outcomes for Study 200812

	Study 200812	
	FF/UMEC/VI 100/62.5/25 N = 527	FF/VI + UMEC 100/25 + 62.5 N = 528
Pulmonary Function		
Baseline FEV_1 Mean (SD)	1.15 (0.448)	1.19 (0.448)
N with analyzable data at week 24 (mPP)	307	287
LS mean change from baseline trough FEV_1 [a,b] (SE)	0.113 (0.0112)	0.095 (0.0116)
Difference [a,b] (95% CI)	0.018 (–0.013 to 0.050)	
N with analyzable data at week 24 (ITT)	436	434
LS mean change from baseline trough FEV[b] (SE)	0.11 (0.010)	
Difference[b] (95% CI)	0.026 (–0.002 to 0.053)	
Moderate or Severe Exacerbations		
Experienced a moderate or severe exacerbation, n (%)	129 (24)	142 (27)
Probability of experiencing a moderate or severe COPD exacerbation, % (95% CI)	25.2 (21.6 to 29.2)	26.8 (23.2 to 30.8)
Time to first on-treatment moderate or severe exacerbation hazard ratio (95% CI)	0.87 (0.68 to 1.12)	
SGRQ		
Baseline mean (SD)	49.0 (15.5)	48.5 (15.9)
N with analyzable data at week 24 (ITT)	489	483
LS mean change from baseline SGRQ total score[c] (SE)	–5.8 (0.59)	–4.9 (0.59)
Difference (95% CI)	–0.9 (–2.54 to 0.73)	
Baseline Dyspnea Index Focal Score		
Mean (SD)	6.4 (2.00)	6.33 (1.96)
Transition Dyspnea Index Focal Score		
N with analyzable data at week 24 (ITT)	482	481
LS Mean (SE)	2.029 (0.1252)	1.892 (0.1254)
Difference (95% CI)	0.137 (–0.211 to 0.485)	

CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second; FF = fluticasone furoate; ITT = intent to treat; LS = least squares; mPP = modified per protocol; SD = standard deviation; SE = standard error; SGRQ = St. George's Respiratory Questionnaire; UMEC = umeclidinium; VI = vilanterol.

Note: Multiplicity not controlled.

[a] Modified per-protocol population; FF/UMEC/VI = 478, FF/VI + UMEC = 478.

[b] Analysis performed using a repeated measures model with covariates of baseline FEV_1, stratum (number of long-acting bronchodilators used during the run-in period: 0/1 or 2), visit number, geographical region, treatment, visit by baseline interaction, and visit by treatment interaction.

[c] Analysis performed using a repeated measures model with covariates of baseline SGRQ, stratum (number of long-acting bronchodilators used during the run-in period: 0/1 or 2), visit number, geographical region, treatment, visit by treatment, and visit by baseline interaction.

Source: CSR for Study 200812.[9]

Harms

Only those harms identified in the review protocol are reported here (see 2.2.1, Protocol). See Table 10 for detailed harms data.

Adverse Events

Within each trial, adverse events were similar across treatment arms. In FULFIL, at 24 weeks adverse events were reported in 38.9% and 37.7% of patients in the FF/UMEC/VI and BUD/FOR arm, respectively. In IMPACT, at 52 weeks, adverse events were reported in 68% to 70% of patients in each arm. In Study 200812, at 24 weeks adverse events were reported in 28% of patients in each arm. The most common adverse event related to upper respiratory tract infections (URTI) or viral URTI; this similarly affected patients in the treatment arms with 10% to 13% of patients experiencing viral URTI within IMPACT and Study 200812, and 2% to 7% experiencing URTI across all trials. Adverse events that occurred in 2% or more of the population are presented in Table 10.

Serious Adverse Events

Within each trial, serious adverse events were similar across treatment arms. In FULFIL, at 24 weeks serious adverse events were reported in 5% and 6% of patients in the FF/UMEC/VI and BUD/FOR arm, respectively. In IMPACT, at 52 weeks, adverse events were reported in 21% to 23% of patients in each arm. In Study 200812, at 24 weeks adverse events were reported in 10% and 11% of patients in the FF/UMEC/VI and FF/VI + UMEC arm, respectively. The most common severe adverse event was related to respiratory, thoracic, and mediastinal disorders and affected 1% to 5% of patients across trial arms in FULFIL and IMPACT. Other serious adverse events that affected 2% or more of the patients per trial arm included COPD, infections and infestations, and pneumonia. Serious adverse events that occurred in 2% or more of the population are presented in Table 10.

Withdrawals Due to Adverse Events

Within each trial, withdrawals due to adverse events were similar across treatment arms. In FULFIL, at 24 weeks withdrawals due to adverse events were reported in 3% of patients in each arm, respectively. In IMPACT, at 52 weeks, withdrawals due to adverse events were reported in 6% to 8% of patients in each arm. In Study 200812, at 24 weeks adverse events were reported in 3% and 2% of patients in the FF/UMEC/VI and FF/VI + UMEC arm, respectively. The most common withdrawal due to adverse events was related to respiratory, thoracic, and mediastinal disorders and affected 1% to 5% of patients across trial arms in FULFIL and IMPACT. Other reasons for withdrawals due to adverse events that affected 2% or more of the patients per trial arm included COPD. Withdrawals due to adverse events are presented in Table 10.

Mortality

In each trial, 1% to 2% of patients died. In FULFIL, four deaths (less than 1%) in the FF/UMEC/VI arm and six deaths (less than 1%) in the BUD/FOR arm occurred by week 24. In the extension of 52 weeks, two additional deaths occurred in the FF/UMEC/VI arm. None of the deaths that occurred in FULFIL were reported to be related to the study drug. The most common causes of death related to cardiovascular conditions (i.e., sudden cardiac death, stroke, cardiac failure). In IMPACT, deaths occurred in 2% of patients in

each trial arm at 52 weeks. Most deaths related to respiratory, thoracic, and mediastinal disorders (including COPD) and cardiac disorders. In Study 200812, deaths occurred in four patients (less than 1%) in each trial arm. None of the deaths that occurred in Study 200812 were reported to be related to the study drug. The most common causes of death related to COPD and pneumonia.

Notable Harms

Anticholinergic syndrome affected each arm similarly across trials. In FULFIL, anticholinergic syndrome occurred in 1.8% and 1.9% of patients in the FF/UMEC/VI and BUD/FOR arm, respectively by week 24. In IMPACT, at week 52, anticholinergic syndrome occurred in 4% of patients in the FF/UMEC/VI arm, and in 3% of patients in both the FF/VI and UMEC/VI arms. In Study 200812, anticholinergic syndrome occurred in 2% and less than 1% in the FF/UMEC/VI and FF/VI + UMEC arms, respectively. Cardiovascular effects affected each arm similarly across trials. In FULFIL, cardiovascular effects occurred in 4.3% and 5.2% of patients in the FF/UMEC/VI and BUD/FOR arm, respectively by week 24. In IMPACT, at week 52, cardiovascular effects occurred in 10% to 11% of patients across trial arms. In Study 200812, cardiovascular effects occurred in 2% and 3% in the FF/UMEC/VI and FF/VI + UMEC arms, respectively. Pneumonia affected each arm similarly across trials, with the exception of BUD/FOR in FULFIL, where pneumonia occurred in 0.8% of patients compared with 2.2% of patients treated with FF/UMEC/VI.

Table 10: Harms

	FULFIL		IMPACT			Study 200812	
	FF/UMEC/VI 100/62.5/25 N = 911	BUD/FOR 400/12 N = 899	FF/UMEC/VI 100/62.5/25 N = 4151	FF/VI 100/25 N = 4134	UMEC/VI 62.5/25 N = 2070	FF/UMEC/VI 100/62.5/25 N = 527	FF/VI + UMEC 100/25 + 62.5 N = 528
AEs							
Patients with > 0 AEs, N (%)	354 (38.9)	339 (37.7)	2,897 (70)	2,800 (68)	1,429 (69)	255 (48)	253 (48)
Most common AEs[a]							
Viral URTI			521 (13)	479 (12)	223 (11)	56 (11)	52 (10)
COPD	15 (2)	23 (3)	455 (11)	472 (11)	279 (13)	23 (4)	31 (6)
URTI	20 (2)	19 (2)	299 (7)	283 (7)	117 (6)	18 (3)	24 (5)
Pneumonia	19 (2)	7 (< 1)	298 (7)	264 (6)	93 (4)	14 (3)	18 (3)
Headache	44 (5)	53 (6)	233 (6)	198 (5)	103 (5)	32 (6)	33 (6)
Back pain	19 (2)	18 (2)	148 (4)	140 (3)	83 (4)	13 (2)	8 (2)
Bronchitis			152 (4)	130 (3)	73 (4)	9 (2)	7 (1)
Oral candidiasis			161 (4)	146 (4)	41 (2)		
Cough			145 (3)	117 (3)	58 (3)	5 (< 1)	8 (2)
Arthralgia	17 (2)	13 (1)	122 (3)	86 (2)	46 (2)		
Sinusitis			104 (3)	98 (2)	45 (2)		
Dyspnea			82 (2)	95 (2)	52 (3)		
Nasopharyngitis	64 (7)	43 (5)					
Pharyngitis	15 (2)	9 (1)				12 (2)	16 (3)
Influenza						17 (3)	18 (3)
Hypertension						8 (2)	11 (2)
SAEs							
Patients with	49 (5)	51 (6)	895 (22)	850 (21)	470 (23)	52 (10)	57 (11)

	FULFIL		IMPACT			Study 200812	
	FF/UMEC/VI 100/62.5/25 N = 911	BUD/FOR 400/12 N = 899	FF/UMEC/VI 100/62.5/25 N = 4151	FF/VI 100/25 N = 4134	UMEC/VI 62.5/25 N = 2070	FF/UMEC/VI 100/62.5/25 N = 527	FF/VI + UMEC 100/25 + 62.5 N = 528
> 0 SAEs, N (%)							
Most common SAEs[b]							
Respiratory, thoracic, and mediastinal disorders	13 (1)	25 (3)	[redacted]	[redacted]	[redacted]	22 (4)	33 (6)
COPD	12 (1)	21 (2)	443 (11)	450 (11)	269 (13)	21 (4)	30 (6)
Infections and infestations	15 (2)	7 (< 1)	[redacted]	[redacted]	[redacted]	13 (2)	19 (4)
Pneumonia	9 (1)	7 (< 1)	184 (4)	152 (4)	54 (3)	8 (2)	12 (2)
WDAEs							
WDAEs, N (%)	28 (3)	25 (3)	252 (6)	327 (8)	187 (9)	18 (3)	11 (2)
Most common reasons							
Respiratory, thoracic, and mediastinal disorders	11 (1)	11 (1)	[redacted]	[redacted]	[redacted]		
COPD	7 (< 1)	2 (< 1)	65 (2)	93 (2)	72 (3)	3 (< 1)	4 (< 1)
Deaths							
Number of deaths, N (%)	4 (< 1)	6 (< 1)	68 (2) the	76 (2)	49 (2)	4 (< 1)	4 (< 1)
Most common reasons							
Respiratory, thoracic, and mediastinal disorders			[redacted]	[redacted]	[redacted]		
Cardiac disorders	0	4 (< 1)	[redacted]	[redacted]	[redacted]		
Notable Harms, N (%)							
Anticholinergic syndrome	16 (1.8)	17 (1.9)	184 (4)	140 (3)	70 (3)	12 (2)	5 (< 1)
CV effects	39 (4.3)	47 (5.2)	450(11)	430 (10)	224 (11)	30 (6)	28 (5)
Local steroid effects	19 (2.1)	24 (2.7)	337 (8)	301 (7)	108 (5)	12 (2)	14 (3)
Pneumonia	20 (2.2)	7 (0.8)	317 (8)	292 (7)	97 (5)	14 (3)	21 (4)

AE = adverse event; BUD = budesonide; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; FF = fluticasone furoate; FOR = formoterol fumarate; SAE = serious adverse event; UMEC = umeclidinium; URTI = upper respiratory tract infections; VI = vilanterol.

WDAEs = withdrawal due to adverse events.

[a] Frequency ≥ 2%.

[b] Frequency ≥ 1%.

Source: CSRs for FULFIL,[7] IMPACT,[8] Study 200812.[9]

Discussion

Summary of Available Evidence

The evidence presented in this review was acquired from three manufacturer-sponsored phase III RCTs. In the 24-week FULFIL trial, patients were randomized in a 1:1 ratio for treatment with FF/UMEC/VI 100/62.5/25 mcg via the Ellipta once daily in the morning and placebo via the Turbuhaler twice daily, or treatment with BUD/FOR 400/12 mcg via the Turbuhaler twice daily and placebo via the Ellipta once daily in the morning. In the 52-week IMPACT trial, patients were randomized in a 2:2:1 ratio for once daily treatment via the Ellipta with FF/UMEC/VI 100/62.5/25 mcg, FF/VI 100/25 mcg, or UMEC/VI 62.5/25 mcg, respectively. In the 24-week Study 200812, patients were assigned to study arms in a 1:1 ratio for treatment with FF/UMEC/VI 100/62.5/25 mcg via the Ellipta once daily in the morning and placebo via the Ellipta once daily in the morning, or treatment with FF/VI 100/25 mcg via the Ellipta once daily in the morning and UMEC 62.5 mcg via the Ellipta once daily in the morning. All trials were similar with respect to inclusion and exclusion criteria. The only difference in inclusion criteria related to FEV_1 and exacerbation history. FULFIL required either a post-bronchodilator FEV_1 of less than 50% predicted normal, or a post-bronchodilator FEV_1 of less than 80% predicted normal and a documented history of two or more moderate exacerbations or one severe (hospitalized) exacerbation in the previous year. In contrast, both IMPACT and Study 200812 required either a post-bronchodilator FEV_1 of less than 50% predicted normal and a documented history of one or more moderate or severe COPD exacerbation in the previous 12 months, or a post-bronchodilator FEV_1 of ≥ 50% and less than 80% of the predicted normal and a documented history of two or more moderate exacerbations or a documented history of one or more severe (hospitalized) COPD exacerbation in the previous year.

The change from baseline in trough FEV_1 was evaluated as a co-primary outcome (at week 24) in FULFIL, the primary outcome (at week 24) in Study 200812, and as a secondary outcome (at week 52) in IMPACT. Trough FEV_1 is recognized as a component of the GOLD classification of airflow limitation severity in COPD.[10] The generally accepted clinically important change in FEV_1 is between 0.10 L and 0.14 L.[35] The change from baseline in the SGRQ total score (at week 24) was evaluated as a co-primary outcome in FULFIL, an “other” outcome (at week 52) in IMPACT, and a secondary outcome (at week 24) in Study 200812. A higher score on the SGRQ indicates a poorer level of health-related quality of life and decreases in score are indicative of improvement in health-related quality of life. A decrease of four points is considered a clinically meaningful improvement. The annual rate of on-treatment moderate or severe exacerbations was evaluated as a primary outcome in IMPACT and a secondary outcome in FULFIL. Potential exacerbations were identified by symptoms reported by patients in an eDiary, followed by confirmation from the investigator. A moderate exacerbation was defined as requiring treatment with oral/systemic corticosteroids and/or antibiotics (not involving hospitalization). A severe exacerbation required in-patient hospitalization. The primary efficacy analysis used modified ITT methodology for FULFIL and IMPACT. Study 200812 was a noninferiority trial, and used a modified per-protocol population for the assessment of the primary efficacy outcome (change from baseline in trough FEV_1) and a noninferiority margin of 0.050 L, where noninferiority was determined if the lower bound of the two-sided 95% CI around the treatment difference was above −0.050 L.

The proportion of patients who discontinued each trial was balanced between trial arms. IMPACT had the highest proportion, where 11% to 14% of patients discontinued compared with 5% to 6% seen in the other trials; this is expected, as IMPACT was 52 weeks in duration and the other trials were 24 weeks. Study discontinuation was most often attributed to withdrawal of consent (1% to 6% across trial arms).

Interpretation of Results

Efficacy

Across the studies, the trough FEV_1 was used to assess pulmonary function. Symptoms (related to pulmonary function) were identified as important based on the patient input. In FULFIL, the within-group improvement in FEV_1 would be considered clinically relevant for FF/UMEC/VI, but not for BUD/FOR. Further, for the comparison between FF/UMEC/VI and the active comparator BUD/FOR, the difference in improvement in trough FEV_1 from baseline were statistically and clinically significant at week 24. A sensitivity analysis that included data from patients who discontinued the study treatment produced similar results to the primary analysis, where improvements with FF/UMEC/VI were seen compared with BUD/FOR, thereby supporting the results of the primary efficacy analysis for trough FEV_1. In IMPACT, the within-group improvement in FEV_1 was not clinically significant for FF/UMEC/VI, or for the active comparator FF/VI. Further, for the comparison between FF/UMEC/VI and the active comparator FF/VI, the difference in improvement in trough FEV_1 from baseline was statistically but not clinically significant at 52 weeks. There was also an improvement in trough FEV_1 from baseline for the comparison between FF/UMEC/VI and UMEC/VI, although the between-group difference was modest (0.054 L; 95% CI: 0.039 to 0.069); this comparison was not included in the hierarchical statistical analysis plan and therefore not adjusted for multiple comparisons. In Study 200812, the improvement for FF/UMEC/VI compared with FF/VI + UMEC was noninferior based on a margin of 0.050 L. Thus, the triple combination of FF/UMEC/VI is no worse than FF/VI + UMEC as separate inhalers for improving trough FEV_1, which is to be expected, and this serves to demonstrate that there is a clinical rationale for the triple combination product if patients require such a regimen. A “tipping point” sensitivity analysis was conducted to explore the impact of missing data (using multiple imputation) by using differing assumptions regarding the mean treatment effect for FEV_1. The results of the tipping point analysis suggested that the conclusions from the study were unlikely to be influenced to a marked degree based on missing data from patients who withdrew prematurely. However, as Study 200812 was designed only to estimate noninferiority between interventions with respect to changes from baseline in trough FEV_1 and all other comparisons for other outcomes were descriptive only, this study does not add to our understanding of the comparative efficacy of FF/UMEC/VI versus other treatment options, particularly other triple drug regimens.

Exacerbations were a key efficacy outcome for the CDR review. Annualized exacerbation rates were the primary outcome of IMPACT; however, the study comparators were UMEC/VI and FF/VI. The lack of a study designed to examine differences in exacerbation rates between FF/UMEC/VI and another LAMA/ICS/LABA comparator is a limitation of the reviewed data. In IMPACT, the annual rate of on-treatment moderate or severe exacerbations and the time to first moderate or severe exacerbation were statistically significantly improved for treatment with FF/UMEC/VI as compared with both FF/VI and UMEC/VI at week 52. For the annualized exacerbation analysis, a sensitivity analysis that included data from patients who discontinued the study treatment produced similar results

to the primary analysis, where improvements with FF/UMEC/VI were seen compared with FF/VI and UMEC/VI. The annual rate of moderate or severe exacerbations and the time to first moderate or severe exacerbation were lower in the FF/UMEC/VI-treated patients as compared with the BUD/FOR-treated patients at 24 weeks in FULFIL; however, this must be interpreted with caution because the duration of the study was shorter than the recommended minimum of one year and this outcome was not adjusted for multiplicity. Exacerbations are a key cost driver and, according to the patient group input submitted to CDR, exacerbations are of major concern to patients. Exacerbations can lead to hospitalizations, which put patients, many of whom are elderly, at risk of acquiring nosocomial infections such as pneumonia, and they are already at higher risk of experiencing morbidity and death from pneumonia. Exacerbations may also lead to the use of systemic corticosteroids, accompanied by a long list of serious adverse effects. Exacerbations were a key efficacy outcome for the CDR review.

Health-related quality of life assessed via the SGRQ was statistically significantly improved for treatment with FF/UMEC/VI (based on the results of FULFIL and IMPACT), and not statistically different from treatment with FF/VI + UMEC (based on the results from Study 200812). Clinically significant changes from baseline for SGRQ were observed for treatment groups in FULFIL and with FF/UMEC/VI only in IMPACT; however, none of the between-group comparisons in either study were considered clinically significant. In both FULFIL and IMPACT, the within-group improvement in SGRQ would be considered clinically meaningful for FF/UMEC/VI based on an MCID of 4.0. In FULFIL, in the active comparator arm BUD/FOR, the within-group improvement in SGRQ was also clinically meaningful. However, in IMPACT in the active comparator arm FF/VI, the within-group improvement in SGRQ was not clinically meaningful. In both FULFIL and IMPACT, the proportion of patients who were SGRQ responders was greater in the FF/UMEC/VI arm compared with the active comparators. Statistical assessment of the EQ-5D-5L was not performed. Health-related quality of life was an outcome identified as important based on the patient input.

Health status and disease impact were assessed in FULFIL and IMPACT using the CAT; this showed improvement for patients treated with FF/UMEC/VI compared with control treatments in these trials, but the comparisons were not adjusted for multiplicity.

Dyspnea was assessed in all trials using the TDI focal score. Improvements were found for treatment with FF/UMEC/VI compared with BUD/FOR (FULFIL) and FF/VI (IMPACT) but not for UMEC/VI (IMPACT). Treatment with FF/VI + UMEC/VI was found to be not statistically different from treatment with FF/UMEC/VI (Study 200812).

A limitation of the reviewed studies was the choice of comparator treatments, specifically the apparent emphasis on comparison with ICS/LABA in two of three studies. ICS/LABA (BUD/FOR) was the only comparator treatment in FULFIL, and in IMPACT the comparators were ICS/LABA and LAMA/LABA, but the drugs were the components of the intervention. Patients in FULFIL were generally GOLD grade 2 (airflow limitation: moderate, post-bronchodilator FEV_1 per cent predicted of ≥ 50% and < 80%) and Group D (CAT ≥ 10 and ≥ 2 moderate or severe exacerbations or ≥ 1 moderate or severe exacerbations leading to hospitalization in the past year), and those in IMPACT were generally GOLD grade 3 or 4 (airflow limitation: severe or very severe, post-bronchodilator FEV_1 per cent predicted < 50%) and Group D, or GOLD grade 2 and Group D.[10] Based on current recommendations from GOLD and CTS, the most appropriate comparator would be dual bronchodilation with LAMA/LABA. LAMA/LABA combination therapy appears to be more effective than

bronchodilator monotherapy and ICS/LABA combination for preventing and decreasing exacerbations, respectively, among patients with a history of exacerbations.[1,10] IMPACT, as mentioned, did include a LAMA/LABA treatment group who received UMEC/VI; FF/UMEC/VI statistically significantly reduced the annualized rate of moderate or severe exacerbations and delayed the time to first moderate or severe exacerbation versus UMEC/VI. The clinical significance of the between-group difference is uncertain, at least in part because the analysis was conducted over the minimum duration of follow-up for evaluating exacerbations in a COPD clinical trial (one year). It is acknowledged that, in the COPD patient populations included in FULFIL and IMPACT, there may have been a subset of patients who, according to evidence-informed guidance from GOLD and CTS, may have been appropriate for LABA/ICS therapy. This group is thought to be those patients with an asthma component. The definition of this particular subpopulation is still uncertain.

Patients were excluded from the trials if they were reported to have a current diagnosis of asthma; it is unclear whether the diagnosis of asthma was confirmed via spirometry and documented for these patients. Post-bronchodilator reversibility was assessed in all randomized patients in each study: reversibility (i.e., an increase in post-bronchodilator FEV_1 of 12% or more and 0.200 L or more) was confirmed in 14% to 20% of patients across all three trials. Patients who demonstrate reversibility may be more likely to respond better to ICS. The proportions of patients with reversibility were balanced between trial arms and therefore their inclusion would not likely create a meaningful differential impact on the efficacy results. However, assessment of pre-specified subgroup analyses by reversibility status may have aided in interpreting the results of the included studies, especially if information related to treatments received just prior to randomization was included in the analysis. [redacted]. While COPD and asthma are distinct diseases, the CTS has reported on the growing recognition that approximately one-quarter to one-third of patients with COPD present with features of asthma (referred to as ACO).

The once daily dosing of FF/UMEC/VI, as well as the design of the inhaler device itself (known as the Ellipta), are claimed by the manufacturer to confer potential advantages when it comes to patient adherence. However, adherence was high in all included studies, and was at least 97% in FULFIL, which compared FF/UMEC/VI to BUD/FOR, and there was no difference in adherence between groups. The other studies compared FF/UMEC/VI to its components administered by the Ellipta device. Adherence is typically high in clinical trials, where patients are closely monitored and are usually a motivated population more likely to follow instruction. Therefore, with the high adherence in treatment groups, there is no way of knowing whether the Ellipta design will indeed lead to better adherence based on the reviewed studies. It is widely accepted that a once daily frequency of administration is preferred by patients and that, the more frequent the administration, the more likely adherence is to suffer. Although there is some evidence of patient preference for the Ellipta over other devices,[46-48] the impact of this preference on patient adherence is unclear and requires direct comparative evidence from well-conducted RCTs and long-term observational studies.

Two supplementary trials were assessed that evaluated the efficacy and safety of adding UMEC (62.5 mg and 125 mg) to FF/VI (Appendix 6). These 12-week trials determined that adding UMEC to FF/VI provided statistically significant improvements in pulmonary function

and similar harms compared with placebo and FF/VI. The relatively short duration of these studies limits the conclusions that can be drawn on the findings.

As mentioned, an important limitation of the included studies was the relatively short durations. The FULFIL extension study (Appendix 7) included a subset of the first 430 patients randomized to treatment in the main randomized period and who gave consent to continue into the extension period, who were treated with FF/UMEC/VI or BUD/FOR for an additional 28 weeks (total of 52 weeks). The extension study suggested that FF/UMEC/VI continued to be superior to BUD/FOR with respect to changes in trough FEV_1, annual rate of moderate or severe exacerbations, and HRQL (based on SGRQ total score). The occurrence of adverse events was similar between groups in the extension phase. However, it is not clear if the design truly preserved randomization between treatment groups, as there were some differences in the characteristics of the treatment groups, and the relatively small sample sizes limits conclusions that can be drawn from this extension phase.

One NMA provided by the manufacturer was assessed (Appendix 8). This NMA compared [redacted]

The quality of the IDC was [redacted]

Harms

It is unclear if the 24-week trials (FULFIL and Study 200812) were of sufficient duration to be able to assess clinically important adverse events such as pneumonia and cardiovascular events. Within each trial, serious adverse events were similar across treatment arms. In FULFIL, at 24 weeks, serious adverse events were reported in 5% and 6% of patients in the FF/UMEC/VI and BUD/FOR arm, respectively. In IMPACT, at 52 weeks, adverse events were reported in 21% to 23% of patients in each arm. In Study 200812, at 24 weeks, adverse events were reported in 10% and 11% of patients in the FF/UMEC/VI and FF/VI + UMEC arm, respectively. The most common severe adverse event was related to respiratory, thoracic, and mediastinal disorders, COPD, infections and infestations, and pneumonia.

Anticholinergic syndrome affected each arm similarly across trials. In FULFIL, anticholinergic syndrome occurred in 1.8% and 1.9% of patients in the FF/UMEC/VI and BUD/FOR arm, respectively, by week 24. In IMPACT, at week 52, anticholinergic syndrome occurred in 4% of patients in the FF/UMEC/VI arm, and in 3% of patients in both the FF/VI and UMEC/VI arms. In Study 200812, anticholinergic syndrome occurred in

2% and less than 1% in the FF/UMEC/VI and FF/VI + UMEC arms, respectively. Cardiovascular effects affected each arm similarly across trials. In FULFIL, cardiovascular effects occurred in 4.3% and 5.2% of patients in the FF/UMEC/VI and BUD/FOR arm, respectively, by week 24. In IMPACT, at week 52, cardiovascular effects occurred in 10% to 11% of patients across trial arms. In Study 200812, cardiovascular effects occurred in 2% and 3% in the FF/UMEC/VI and FF/VI + UMEC arms, respectively. Pneumonia affected each arm similarly across trials, with the exception of BUD/FOR in FULFIL, where pneumonia occurred in 0.8% of patients compared with 2.2% of patients treated with FF/UMEC/VI.

The manufacturer-provided NMA [redacted].

Potential Place in Therapy[2]

International and Canadian recommendations have been reconsidering the approach to COPD management since 2013 to take into consideration new studies and new molecules that have been emerging in the field of COPD management. Decreasing exacerbation rates, especially exacerbation leading to emergency room visits and/or leading to hospitalizations, has been a cornerstone of the therapeutic approach and has been influencing clinical recommendations, in particular in the GOLD document. Another shift that has been happening is in the way patients are evaluated. Patient-centred therapy requires physiological markers and appropriate disease definition. In the case of COPD, for many years now there have been discussions as to which COPD patients would benefit from “triple therapy” (LAMA/LABA/ICS). The recognized increased risk of pneumonia in certain COPD patients using ICS led to attempts at better phenotyping patients. It is estimated in the current literature that about 25% to 30% of COPD patients benefit from the added ICS treatment. There is also research interested in trying to identify what defines the 25% to 30% of patients who benefit from LAMA/LABA/ICS. Whether a composite set of clinical features (e.g., history of asthma, normal diffusion capacity, minimal smoking history, etc.) or whether one specific marker (e.g., elevated peripheral eosinophils, sputum eosinophils, etc.) is the answer is still unclear. Nonetheless, research is focusing on this area because the cost associated with ICS in the treatment of COPD is high, and because the complications (especially the rates of pneumonia) are significant and clinically relevant.

The new international and Canadian guidelines recommend bronchodilation and dual bronchodilation at the forefront of the therapeutic approach for COPD: bronchodilators are recommended as first-line treatment for symptomatic patients from GOLD group A to D. Triple therapy (LAMA/LABA/ICS) is currently considered in patients with recurrent exacerbations despite dual bronchodilation. Even in this category of patients, adverse effects of corticosteroids should be monitored and especially patients developing radiologically proven pneumonia while on ICS should have their treatment approach reviewed.

A new concept in the management of COPD introduced in both GOLD 2017 and CTS 2017 is the concept of “step-up” and “step-down” approach to management. A patient who is “stepped-up” to dual bronchodilation or on triple therapy in whom no improvement is noted (i.e., no change in symptoms or exercise tolerance or exacerbation rate) could “step down” to the previous therapeutic regimen. The step-down concept allows all physicians to review patient “stability” and minimize pharmacological treatments.

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

Conclusions

Three phase III manufacturer-sponsored RCTs were included in this review: two 24-week trials (FULFIL and Study 200812) and one 52-week trial (IMPACT). In the assessment of pulmonary function, treatment with FF/UMEC/VI showed statistically significant improvements in trough FEV_1 for comparisons with BUD/FOR at 24 weeks, FF/VI at 52 weeks, and UMEC/VI at 52 weeks. Clinical significance was achieved for the comparison with BUD/FOR at 24 weeks. Compared with its components, FF/UMEC/VI was noninferior based on a 0.050 L margin, where noninferiority was determined if the lower bound of the two-sided 95% CI around the treatment difference was above −0.050 L. Health-related quality of life was assessed via the SGRQ; improvements were identified for treatment with FF/UMEC/VI compared with BUD/FOR at 24 weeks, FF/VI at 52 weeks, and UMEC/VI at 52 weeks. FF/UMEC/VI was not statistically different from treatment with its components for changes in SGRQ. The annual rate of on-treatment moderate and severe exacerbations was improved for treatment with FF/UMEC/VI compared with treatment with BUD/FOR at 24 weeks, FF/VI at 52 weeks, and UMEC/VI at 52 weeks. FF/UMEC/VI was found to be not statistically different from treatment with its components on moderate or severe exacerbations. A manufacturer-provided NMA suggested that the efficacy of FF/UMEC/VI was not statistically different from other triple therapies for several outcomes, including changes in trough FEV_1 and SGRQ total score, and in annual rates of moderate or severe exacerbations. However, several limitations with the analysis mean that results are associated with considerable uncertainty.

Adverse events were generally similar between FF/UMEC/VI and the other treatment arms in the three RCTs; however, the durations of the studies were likely too short to draw clear inferences on the comparative rates of pneumonia and CV events. The reviewed NMA did not evaluate the comparative safety of FF/UMEC/VI with other triple therapies for COPD.

Appendix 1: Patient Input Summary

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

One patient group provided input. COPD Canada is a non-profit organization that has helped to inform and support Canadians living with chronic obstructive pulmonary disease (COPD) since its inception in 2005. COPD Canada acts as both an educational association and a patient advocacy group. It provides patient education materials and services, and produces quality of life seminars for patients and their families. The organization reviews and interprets scientific literature related to emphysema and chronic bronchitis so that it can be easily interpreted by the community. COPD Canada composes the COPD Digest from relevant scientific and medical literature and distributes it to relevant members of the Canadian medical profession, government agencies, non-profit organizations, and other health care personnel. Members of COPD Canada consist of patients with COPD and their caregivers. Membership is free of charge but is restricted to COPD patients and their caregivers.

Within the last two years, COPD Canada received financial payments from AstraZeneca Canada, GSK Canada (GlaxoSmithKline), and Novartis Canada. COPD Canada declared no outside help or financial payment in the compiling of this submission.

2. Condition-Related Information

COPD Canada collected Canadian-applicable patient input from the personal experiences of the organization's members and published scientific articles. Members of COPD Canada provided their experiences during group pulmonary rehabilitation sessions, lung issue support groups, as well as in direct one-on-one consultations. Also, COPD Canada distributed an email survey in February 2018, for which they received 44 written responses.

COPD has a profound effect on patients' lives as well as their caregivers. COPD is associated with a considerable burden of disease, affecting many things that are fundamental to everyday life, such as the ability to breath, talk, sleep, work, and socialize. As the disease progresses and worsens, patients become less physically active and more socially isolated. Many patients with COPD are of working age, so even in the early stages of the disease, the breathlessness and fatigue caused by COPD reduces the ability of the patient to go to work or carry out normal work activities. Some patients are forced to go into early retirement as a consequence of the severity of the progressive disease.

Even many of the day-to-day activities most take for granted are virtually impossible or extremely difficult for people with severe COPD. Changing bed sheets, bathing and dressing, shopping and carrying bags and groceries, climbing stairs, and walking and talking at the same time are all examples of such day-to-day activities.

To adapt, patients' lifestyles are forced to change in a variety of ways, including avoiding public places or toilets that are not located on the ground floor, having to continuously use supplemental oxygen, continually being concerned with weather conditions, avoiding any exertion outdoors particularly during cold or hot weather, and having to walk at a slow pace.

Caregivers face considerable challenges that commonly include limited time for managing their health and well-being, feelings of depression and isolation, anxiety, stress, fatigue, feeling of unending days, and increased requirements for social support. In the case of grown children who become their parent's caregivers, they are often torn between the

needs of their young families and the needs of their elderly parent with COPD. From a 68-year-old male in British Columbia:

> "Most important to control breathing. My day-to-day life is radically changed. I take 200% more time to accomplish a task than before I had COPD. The activities I cannot perform are walking, woodworking, driving, cooking, and general day-to-day tasks. The drugs that I currently use are Spiriva, Advair, Ventolin, and I am on a 4 L per minute O_2 flow all the time. (My FEV_1 is 33%.) The effectiveness is marginal. All of my specialists are in Victoria, 1,100 km away. Impact on my wife is tremendous, as she has to devote a lot of time to me and my needs now."

3. Current Therapy-Related Information

There is no cure for COPD, and there are no medications that reverse the loss of lung function caused by COPD. Current therapy for COPD aims to maintain control of symptoms and prevent or minimize the frequency and duration of exacerbations. Typical maintenance therapy usually includes the use of Spiriva once per day with Advair or Symbicort twice per day. Rescue medications vary from patient to patient, although Ventolin is used quite extensively. These products are to control the condition, but they do not improve long-term lung function. When one experiences an exacerbation, Prednisone and antibiotics are often prescribed. Prednisone works quickly but has dangerous side effects. The overuse of antibiotics has become a national and international concern because of increased resistance, particularly in long-term care facilities. From a 73-year-old female Albertan, diagnosed in 2007:

> "I have tried many different drugs. Spiriva, in my opinion, caused extreme blood pressure, which caused uncontrollable nosebleeds. I then tried Advair, Symbicort, Breo. All caused dryness in my throat and long bouts of coughing. I was switched to Ultibro Breezhaler and Seebri but still coughed more than usual and was phlegmy. My lung specialist is at a loss as to what to prescribe. She feels I should go back on Respimat and change to different blood pressure medication."

4. Expectations About the Drug Being Reviewed

Although none of the surveyed patients had direct experience with the drug under review, COPD patients generally need additional therapies that work to improve breathing and lung function, are easy to use, and do not just offer symptomatic or emergency relief. Because COPD is treated in a stepwise manner where treatments are layered on as the disease progresses, additional treatment options are often needed to address continual disease progression, particularly as the disease progresses in severity. As well, long-term use of some of these compounds results in a diminishing of the drug's effectiveness. Availability of alternative but equivalent drugs is desirable.

The patient group considered that any new COPD therapy — like Trelegy Ellipta — that encourages compliance by being simpler to use, is three medications in one dosage, and is used only once per day while decelerating or limiting the need for rescue inhalers, is worthwhile.

COPD Canada is aware of accessibility issues throughout Canada and notes that provincial drug coverage varies considerably among the plans. COPD Canada points out that most of COPD patients are older than 65 years of age and rely on provincial drug coverage.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE ALL 1946 to present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	March 29, 2018
Alerts:	Biweekly search updates until July 18, 2018
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
*	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
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
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.rn	CAS registry number
.nm	Name of substance word
medall	Ovid database code; MEDLINE ALL 1946 to present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
1	(Alisade* or Allermist* or Arnuity* or Avamys* or Flonase Sensimist* or Furamist* or GSK 685 698 or GSK685 698 or GSK685698 or GSK 685698 or GW 685698* or GW685698* or UNII-JS86977WNV or JS86977WNV or Veramyst*).ti,ab,kf,ot,hw,rn,nm.
2	(fluticason* or HSDB 7740 or HSDB7740 or UNII-CUT2W21N7U or CUT2W21N7U).ti,ab,kf,ot,hw,rn,nm.
3	or/1-2
4	*Fluticasone furoate/
5	*Fluticasone/
6	(Alisade* or Allermist* or Arnuity* or Avamy*s or Flonase Sensimist* or Furamist* or GSK 685 698 or GSK685 698 or GSK685698 or GSK 685698 or GW 685698* or GW685698* or Veramyst*).ti,ab,kw,dq.
7	(fluticason* or HSDB 7740 or HSDB7740).ti,ab,kw,dq.
8	or/4-7

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
9	(umeclidinium or Ellipta* or Incruse* or Rolufta* or GSK573719* or GSK-573719* or UNII-GE2T1418SV or GE2T1418SV or UNII-7AN603V4JV or 7AN603V4JV).ti,ab,kf,ot,hw,rn,nm.
10	*Umeclidinium/
11	(umeclidinium or Ellipta* or Incruse* or Rolufta* or GSK573719* or GSK-573719*).ti,ab,kw,dq.
12	or/10-11
13	(vilanterol or GSK 642444 or GSK642444 or GW-642444* or GW642444* or UNII-028LZY775B or 028LZY775B or UNII-DB71X3OVN2 or DB71X3OVN2 or UNII-40AHO2C6DG or 40AHO2C6DG).ti,ab,kf,ot,hw,rn,nm.
14	*Vilanterol/
15	*Vilanterol trifenatate/
16	(vilanterol or GSK 642444 or GSK642444 or GW-642444* or GW642444*).ti,ab,kw,dq.
17	or/14-16
18	((fluticasone furoate adj2 vilanterol) or (dluticasone furoate adj2 vilanterol) or Breo* or Relovair* or Relvar* or Revinty Ellipta* or FFVI or (GW685698 ad GW642444)).ti,ab,kf,ot,hw,rn,nm.
19	*Fluticasone furoate plus vilanterol/
20	((fluticasone furoate adj2 vilanterol) or (dluticasone furoate adj2 vilanterol) or Breo* or Relovair* or Relvar* or Revinty Ellipta* or FFVI or (GW685698 ad GW642444)).ti,ab,kw,dq.
21	or/19-20
22	((umeclidinium adj3 vilanterol) or Noro* or Ellipta* or Avenair* or GSK 573719 or GSK573719).ti,ab,kf,ot,hw,rn,nm.
23	*Umeclidinium plus vilanterol/
24	((umeclidinium adj3 vilanterol) or Noro* or Ellipta* or Avenair* or GSK 573719 or GSK573719).ti,ab,kw,dq.
25	or/23-24
26	(FFUMECVI or (fluticasone furoate adj2 umeclidinium adj2 vilanterol) or Trelegy Ellipta*).ti,ab,kf,ot,hw,rn,nm.
27	(FFUMECVI or (fluticasone furoate adj2 umeclidinium adj2 vilanterol) or Trelegy Ellipta*).ti,ab,kw,dq.
28	3 and 9 and 13
29	9 and 18
30	3 and 22
31	(or/26,28-30) use medal
32	8 and 12 and 17
33	12 and 21
34	8 and 25
35	(or/27,32-34) use emend
36	conference abstract.pt.
37	35 not 36
38	31 or 37
39	remove duplicates from 38

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same keywords, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords used as per MEDLINE search.

Grey Literature

Dates for Search:	March 2018
Keywords:	(Trelegy Ellipta (fluticasone furoate umeclidinium vilanterol) COPD
Limits:	No date or language limits used.

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/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

Table 11: Excluded Studies

Reference	Reason for Exclusion
Baker, 2013[49]	Study design
Cassola and Matera, 2014[50]	Study design
Ullmann et al., 2017[51]	Study design
Sousa et al., 2016[52]	Intervention
Yang et al., 2017[53]	Population

Appendix 4: Detailed Outcomes Data

Table 12: Efficacy Outcomes for IMPACT by [redacted]

	[redacted]			[redacted]		
	FF/UMEC/VI 100/62.5/25 N = [redacted]	FF/VI 100/25 N = [redacted]	UMEC/VI 62.5/25 N = [redacted]	FF/UMEC/VI 100/62.5/25 N = [redacted]	FF/VI 100/25 N = [redacted]	UMEC/VI 62.5/25 N = [redacted]
Pulmonary Function						
Baseline FEV_1 mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change from baseline trough FEV_1 (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]		[redacted]	[redacted]
P value		[redacted]	[redacted]		[redacted]	[redacted]
Moderate/Severe Exacerbations						
Annual model-estimated exacerbation rate[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rate ratio (95% CI)		[redacted]	[redacted]		[redacted]	[redacted]
P value[b]		[redacted]	[redacted]		[redacted]	[redacted]
Time to first on-treatment moderate or severe exacerbation hazard ratio[c] (95% CI)		[redacted]	[redacted]		[redacted]	[redacted]
P value		[redacted]	[redacted]		[redacted]	[redacted]
Baseline Dyspnea Index Focal Score						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Transition Dyspnea Index Focal Score						
LS Mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]		[redacted]	[redacted]
P value		[redacted]	[redacted]		[redacted]	[redacted]
CAT						
Baseline CAT mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]		[redacted]	[redacted]
P value		[redacted]	[redacted]		[redacted]	[redacted]

CAT = COPD assessment test; CI = confidence interval; FEV_1= forced expiratory volume in one second; FF = fluticasone furoate; LS = least squares; SD = standard deviation; SE = standard error; UMEC = umeclidinium; VI = vilanterol.

[redacted]

Table 13: EQ-5D-5L Results for FULFIL

	FULFIL (24 Weeks)		IMPACT (52 Weeks)		
	FF/UMEC/VI 100/62.5/25 N = 911	BUD/FOR 400/12 N = 899	FF/UMEC/VI 100/62.5/25 N = 4,151	FF/VI 100//25 N = 4,134	UMEC/VI 62.5/25 N = 2,070
EQ-5D-5L Utility Index					
Baseline EQ-5D-5L Utility Index mean (SD)	0.8 (0.17)	0.8 (0.17)	0.8 (0.17)	0.8 (0.18)	0.8 (0.18)
N with analyzable data at week 12 for FULFIL, week 52 for IMPACT	875	832	3,277	2,987	1,454
Mean change (SD)	0.0 (0.15)	0.0 (0.15)	0.0 (0.16)	0.0 (0.18)	0.0 (0.16)
EQ-5D-5L VAS Score					
Baseline EQ-5D-5L VAS score mean (SD)	60.2 (16.43)	60.6 (16.41)	65.4 (16.91)	65.2 (16.95)	65.6 (16.72)
N with analyzable data at week 12 for FULFIL, week 52 for IMPACT	875	832	3,277	2,987	1,454
Mean change (SD)	5.8 (17.18)	3.8 (16.34)	5.0 (17.21)	4.6 (17.59)	5.0 (16.91)

BUD = budesonide; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels Questionnaire; FF = fluticasone furoate; FOR = formoterol fumarate; SD = standard deviation; UMEC = umeclidinium; VAS = visual analogue scale; VI = vilanterol.

Source: CSR for FULFIL.[7]

Appendix 5: Validity of Outcomes Measures

Aim

To summarize the validity of the following outcomes measures:

- Chronic Obstructive Pulmonary Disease (COPD) Assessment Test (CAT)
- EuroQol 5-Dimensions 5-Levels Questionnaire (EQ-5D-5L)
- EXAcerbations of Chronic Pulmonary Disease Tool – Respiratory Symptoms (EXACT-RS)
- Forced expiratory volume in one second (FEV_1)
- St. George's Respiratory Questionnaire (SGRQ)
- Transition Dyspnea Index (TDI).

Findings

COPD Assessment Test (CAT)

The CAT is a patient-completed questionnaire designed for use in routine clinical practice to assess the impact of chronic obstructive pulmonary disease (COPD) on a patient's health status.[34] CAT consists of eight items that address the following: cough, phlegm, chest tightness, breathlessness going up a hill or stairs, activity limitation at home, confidence in leaving home, sleep, and energy. Each item is scored on a six-point ordered scale ranging from 0 (no impairment) to 5 (maximal impairment), with a total scale score ranging from 0 to 40 units, where higher scores represent worse health.[34] The CAT developers suggest that a total score of < 10 units relates to low impact on health status, 10 to 20 units as medium impact, 21 to 30 units as high impact, and 30 to 40 units as very high impact.

A published systematic review of validation studies of the CAT in COPD found that it showed adequate internal consistency (Cronbach's alpha = 0.85 to 0.98) in eight studies of 50 to 6,469 patients each, and showed adequate test-retest reliability (intraclass correlation coefficient = 0.80 to 0.96) in five studies of 45 to 377 patients each, with administration durations of two to three weeks.[40] The threshold for adequate internal consistency and test-retest reliability was considered to be 0.70. Ten studies of 45 to 486 patients evaluated responsiveness of the CAT — four in patients undergoing pulmonary rehabilitation (mean change in CAT score −3.0 to −2.2 units, (standard deviation [SD] not reported), one in patients experiencing an exacerbation (score increased by 4.7 units), and five recovering from an exacerbation on-treatment, with improvement in the CAT score up to 12 weeks (−1.4 ± 5.3 to −11.0, SD not reported).[40] The tool appears to be responsive to both improvement and deterioration, but the MCID, to be subsequently discussed, is uncertain.

Convergent validity was studied in 21 studies of 50 to 6,437 patients through comparisons with the COPD-specific questionnaires and clinical measures (Table 14).[40] For the Chronic Respiratory Questionnaire, individual correlations of individual domains were averaged to create an overall correlation. Correlation was moderate to high for most comparisons, with the exception of longitudinal validity in exacerbation recovery.

Table 14: Convergent and Longitudinal Validity for the COPD Assessment Test

Disease-Specific Questionnaire	Number of Studies	Patients/Follow-Up	Convergent Validity	Longitudinal Validity
SGRQ-C	7	Exacerbation recovery, 4 weeks	Pearson's 0.69 to 0.82; Spearman's 0.64	Pearson's 0.63
SGRQ	5	Pulmonary rehabilitation, 8 weeks	Pearson's 0.72 to 0.74; Spearman's 0.65 to 0.84	Pearson's 0.36
CCQ	4	Exacerbation recovery, 6 weeks	Not reported	Pearson's 0.60
CCQ	4	Pulmonary rehabilitation, 8 weeks	Pearson's 0.68 to 0.78	Pearson's 0.13
CRQ	5	Pulmonary rehabilitation, 6 to 8 weeks	Pearson's −0.48 to −0.33	Pearson's −0.50 to −0.38

CCQ = Clinical COPD Questionnaire; COPD = chronic obstructive pulmonary disease; SGRQ = St George's Respiratory Questionnaire.

Source: Gupta et al., 2014.[40]

In the systematic review, four studies of 90 to 575 patients estimated MCID.[40] Three used the anchor-based approach, two of which could not determine an MCID, and the third identified an MCID of −2 units.[39,40] Two studies used the distribution-based approach (standard deviation 0.5), determining MCIDs of 3.76 units, and −3.3 to −3.8 units.[40]

EuroQol 5-Dimensions 5-Levels Questionnaire

The EuroQol 5-Dimensions 5-Levels Questionnaire (EQ-5D-5L) was developed by the EuroQol Group — a network of international multidisciplinary researchers devoted to the measurement of health status. The EQ-5D-5L is a generic, self-reported health status assessment tool that measures the respondent's immediate situation in two parts: the EQ-5D descriptive system and the EQ-visual analogue scale (VAS). The descriptive system consists of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels, ranging from 1 ("No problem") to 5 ("Extreme problems"). Each state is reported as a five-digit code (e.g., 23345), which is interpreted as slight problems with mobility, moderate problems with self-care and usual activities, severe problems with pain/discomfort, and extreme problems with anxiety/depression. EQ-5D health states, which are defined by the descriptive system, can be converted into a single utility index using a weighted formula of utilities specific to population and disease; the summary index can be used to calculate quality-adjusted life-years. The EQ-VAS records the respondent's self-rated health on a vertical VAS, where the end points are 100 "best imaginable health state" and 0 "worst imaginable health state." The EQ-VAS scores are patient-based and not representative of the general population.[54]

The construct validity of the EQ-5D-5L was investigated in a cross-sectional cohort of 625 stable outpatients with COPD, of whom 616 had complete data.[55] Patients were a mean 70.4-years-old, with mean-predicted forced expiratory volume in one second (FEV_1) 46.1%.The EQ-5D-5L, CAT, St. George's Respiratory Questionnaire (SGRQ), Clinical COPD Questionnaire (CCQ), Chronic Respiratory Questionnaire, and Medical Research Council dyspnea scale were measured and severity calculated by the age dyspnea obstruction index. There was moderate correlation between the EQ-5D-5L utility score and the disease-specific total scores and most subscales, with Pearson correlation coefficients with CAT of −0.528, with SGRQ total score of −0.623 (subscales −0.257 to −0.603), with CCQ total of −0.626 (subscales −0.483 to −0.674), and with CRQ total score of 0.709 (subscales 0.403 to 0.593).[55] Correlation with the EQ-VAS was low, with Pearson

correlation coefficients with CAT of −0.428, with SGRQ total score of −0.469 (subscales −0.283 to −0.457), and with CCQ total of −0.483 (subscales −0.382 to −0.459).[55]

The responsiveness of the EQ-5D-5L was investigated in 400 patients undergoing pulmonary rehabilitation, of whom 324 had both baseline and eight-week measurements.[55] Ceiling effects were reported, with 6% and 11% of patients reporting a maximum utility score (1.0) before and after rehabilitation, and 3% and 4% reporting a maximum EQ-VAS score (100.0) before and after rehabilitation, respectively. The standardized response means were 0.39 and 0.44 for the utility scores and EQ-VAS, respectively. Change in EQ-5D-5L utility index and VAS were not considered to be correlated with change in SGRQ total and symptom scores and CAT, with a Pearson correlation coefficient < 0.30. The correlation for change in the EQ-5D-5L utility index and change in the CRQ total score was low, 0.40 (subscales 0.25 to 0.39); the correlation coefficient for change in EQ-VAS and change in CRQ total score was 0.38 (subscales 0.30 to 0.32).[55]

EQ-5D-5L has been validated in a diverse patient population in six countries.[56] The MCID estimates for the index score in the Canadian population have a summarized mean (standard deviation [SD]) of 0.056 (0.011), and a summarized median of 0.056 (interquartile range 0.049 to 0.063).[57] The MCID for the utility index and the EQ-VAS were estimated using a variety of methods, including SD and anchor-derived estimates based on the CRQ total score and mastery and emotion subscales, in the abovementioned patient population.[55] Estimates for the MCID of the EQ-5D-5L utility score ranged from 0.037 (CRQ total, receiver operating characteristic, as anchors) to 0.109 (distribution, 0.5 SD), and those for EQ-VAS from 6.5 (anchored to CRQ total, using ROC methods) to 10.1 (distribution, 0.5 SD).[55]

EXAcerbations of Chronic Pulmonary Disease Tool – Respiratory Symptoms

The EXAcerbations of Chronic Obstructive Pulmonary Disease Tool – Respiratory Symptoms (EXACT-RS) score measures the effect of treatment on the severity of respiratory symptoms of COPD. It is based on the 11 respiratory symptom items of the EXACT — a 14-item, daily patient diary intended to track exacerbations.[58] Besides the Total Score, the EXACT-RS has three symptom subscales: RS-Breathlessness (five items), RS Cough and Sputum (three items), and RS-Chest symptoms (three items). Responses are according to a five-point integer scale with descriptors that vary according to the subscale. Summation of items produces the total score and subscales. The EXACT-RS Total Score ranges from 0 to 40, RS-Breathlessness ranges from 0 to 17, RS-Cough and Sputum ranges from 0 to 11, and RS-Chest symptoms ranges from 0 to 12. In all cases, higher scores indicate more severe symptoms.

Reliability, construct validity, and responsiveness of the EXACT-RS were assessed in a post-hoc analyses of 188 stable patients from a prospective study of COPD, [59] and from three clinical trials (Mpex, AZ 1, and AZ 2) in COPD patients, with available data from 235, 749, and 597 trial patients, respectively.[58] At baseline, the percentage of patients in the prospective study with the modified Medical Research Council (mMRC) dyspnea score 3 or 4 was 29.3%.[59] At baseline, the percentage of trial patients with GOLD stage III or IV was 66.0%, 27.8%, and 44.3% in Mpex, AZ 1, and AZ 2, respectively.[58]

In the three trials, internal consistency for weekly measurements, measured by Cronbach's alpha, was high for RS Total, RS-Breathlessness, and RS-Chest symptoms scales (0.90 to 0.96), and lower for RS-Cough and Sputum (0.58 to 0.78).[58] Reproducibility for weekly measurements, as measured by intra-class correlation, was acceptable, ranging from

0.69 to 0.74 for all scales and trials, with the exception of RS-Cough and Sputum, for the Mpex trial (0.58).[58]

Construct validity was assessed by correlation with measures of health status (SGRQ[58,59]), respiratory symptoms (breathlessness, cough, and sputum scale (BCSS),[58] SGRQ-C,[58] mMRC,[59] airway obstruction (FEV_1),[58,59] and use of rescue medication.[58,59] In the prospective observational study, the EXACT-RS Total Score was highly correlated with the SGRQ Total Score (0.75), and the correlation of the subscales of both with each other was as expected, with correlations of > 0.4 for all except E-RS Cough and Sputum and EXACT-RS-Chest symptoms with SGRQ Activity. Correlation of EXACT-RS and subscales with the mMRC was lower (0.33 and 0.16 to 0.38), as were correlations with rescue medication use, and FEV_1 % Predicted.[59] In the trials, the Total Score was highly correlated with the BCSS Total Score in AZ1 and AZ2 (Spearman's rank order correlation was 0.89 in both), with correlations for individual subdomains of 0.75 to 0.92.[58] EXACT-RS Total Score was correlated with the SGRQ Total Score for the Mpex trial (Spearman's rank order correlation 0.65), with correlations for the individual subdomains of 0.45 to 0.60.[58] The EXACT-RS Total Score was correlated with SGRQ-C in AZ1 and AZ2 (Spearman's rank order correlation 0.51 to 0.54), with correlations for the individual subdomains of 0.41 to 0.52.[58] Correlation of ES-R with FEV_1 was low; for the RS-Breathlessness scale, Spearman's rank order correlation ranged from −0.17 to −0.32. Correlation of the ES-R Total Score and RS-Breathlessness with the use of rescue medication was moderate, with Spearman's rank order correlation ranging from 0.42 to 0.43 in AZ1 and AZ2. The strength of correlation conformed to the authors' pre-specified expectations, leading them to conclude that the construct was valid.

Responsiveness was assessed in the three trials. For patients whose health status improved from baseline to three months (change in SGRQ ≥ 4), EXACT-RS Total Scores declined by an average of −2.5 to −3.5. For those whose symptoms improved (BCSS ≥ 1), EXACT-RS Total Scores declined by an average of −6.[58]

One study of 188 patients used a distributional method (0.5 standard deviation [SD] of the sample mean) to estimate the MCID of the EXACT-RS: RS Total Score, 3.35; RS-Breathlessness,1.85; RS-Cough and Sputum, 1.15; and RS-Chest symptoms, 1.05.[59] In the three trials, 0.5 SD of the sample means were calculated as RS Total Score, 2.97 to 3.00; RS-Breathlessness, 1.56 to 2.97; RS-Cough and Sputum, 0.78 to 1.04; and RS-Chest symptoms, 0.96 to 1.04.[58]

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 both in clinical practice and in clinical trials, and has been correlated with treatment failure (death, intubation, readmission for COPD, or intensification of drug therapy) in hospitalized patients.[60,61] In clinical practice, FEV_1 is used to grade risk of death in COPD patients.[62] The generally accepted clinically important change in FEV_1 is between 0.10 L and 0.14 L.[35] There is evidence that, for patients who are undergoing COPD exacerbation, a two-day increase of 0.10 L reduced the odds of treatment failure (odds ratio 0.80, 95% CI, 0.69 to 0.92).[60]

While both pre- and post-bronchodilator FEV_1 values have been reported to be indicators of health status, risk of death, and measure of severity in COPD, the Global initiative for chronic Obstructive Lung Disease (GOLD) criteria indicates that post-bronchodilator values should be used.[62] This is supported by evidence from a prospective study of 300 patients

with COPD who were followed for at least one and one-half years and who were evaluated every three months until the end of the study.[62] 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. The all-cause mortality $P = 0.008$ versus 0.126, while the respiratory-cause mortality was $P = 0.016$ 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 the pre-bronchodilator per cent-predicted FEV_1 ($P = 0.009$ versus 0.131).

Normalized area under the curve FEV_1 is an average of the measurement of bronchodilation over at least 80% of the duration of action after a single inhalation.[63] No information regarding the MCID was identified.

St. George's Respiratory Questionnaire COPD

The SGRQ is a disease-specific measure of health-related quality of life that was specifically developed for patients with airway obstruction.[64] The COPD-specific version (SGRQ-C) was derived from it, using Rasch analysis of the responses of a sample (n = 893) of COPD patients to identify items with the weakest measurement properties.[45] The number of items was reduced from 50 to 40, corrections were made to reduce disordered responses, wording was modified, and the recall period was no longer specified.[45] The scoring algorithm was revised to produce scores directly comparable to the SGRQ.

The SGRQ-C questionnaire is intended for supervised self-administration. It contains 14 questions and 40 items, grouped into three domains: Symptoms, Activity, and Impacts. Part 1 (seven items) measures the frequency of respiratory symptoms, and contributes to a Symptoms score. For six questions, patients select one response from three to five items; e.g., from “Not at all” to “Most days.” The seventh question has a “yes/no” response. Part 2 (seven items) addresses the patient’s current state, and divides that into an Activity score that measures the effect on daily physical activity, and an Impacts score that addresses psychosocial functioning.[45,65] Two questions have a single response, and for the rest, patients select all the responses that apply.[65] Items are weighted using empirically derived weights. The SGRQ-C Total Score and the three symptom scores are calculated by the summation of the weighted items and the calculation of the percentage of the maximum possible score for the total score or subscale, producing values that range from 0 to 100, where 0 indicates no impairment and 100 indicates worst possible health.[45,66]

Assessment of psychometric properties proceeded throughout the revision process. Correlation between the original SGRQ score and the revised SGRQ score (following removal of items and calculation of rescaling prior to rewording and removal of recall period) was assessed using data from the original SGRQ validation study: 152 patients; mean FEV_1 % predicted, 53.5%. Correlation was very high, with an intraclass correlation coefficient of 0.99.[45]

Construct validity and reliability for the revised SGRQ score were assessed using data from the original SGRQ validation study,[45] against measures for respiratory function (FEV_1 and FVC), physical function (six-minute walk distance), symptoms (Medical Research Council (MRC) dyspnea grade, cough/phlegm, daily wheeze), global health (Sickness impact profile [SIP] and Global Health), and anxiety (Hospital Anxiety and

Depression Scale [HADS] anxiety). Correlation between the revised SGRQ Total Score and the MRC dyspnea grade, and the SGRQ Activity subscale and MRC dyspnea grade, were high (0.70 to 0.72).Moderate correlations were seen between the revised SGRQ Total Score and the HADS anxiety, six-minute walk distance, and Global health (absolute value 0.56 to 0.68), the SGRQ Impacts subscale with six-minute walk test, MRC dyspnea grade, HADs anxiety, SIP total, and Global Health were moderate (absolute value 0.59 to 0.64); and the SGRQ Activity score and the six-minute walk distance, MRC dyspnea grade, SIP total, and Global health (absolute value 0.55 to 0.72). Other correlations were low or absent.[45] Reliability was assessed for this group of patients and a second described further in the section on responsiveness (n = 196) as excellent, SGRQ Total Score 0.99 and 0.98, SGRQ Symptoms 0.96 and 0.93, SGRQ Activity 0.99 and 0.98, and SGRQ Impacts 0.98 and 0.97.[45]

Construct validity and reliability for the SGRQ-C score (following rewording) were assessed for a group of 63 COPD patients involved in pulmonary rehabilitation programs, with a FEV_1 % predicted at 47%.[45] Moderate correlations were seen between the SGRQ Total Score and the HADS depression and Global Health, between the SGRQ-C Activity and MRC dyspnea grades, and between SGRQ Impacts and HADS depression. Correlation was low or not identified for the other measures. The pattern of correlation was similar between the original SGRQ and the SGRQ-C.[45] Reliability for the SGRQ-C score in this group of patients was excellent for Total Score, Activity, and Impacts (0.91 to 0.95), and slightly lower for Symptoms (0.80).

Responsiveness of the revised SGRQ score was assessed using data from a clinical trial of salmeterol versus placebo involving 169 COPD patients, mean age 62 years and FEV_1 % predicted at 46%.[45] Mean change scores were very similar between original and revised SGRQ scores. Greater improvement between baseline and 16 weeks was measured in patients receiving salmeterol, with statistically significant differences between treatment groups for SGRQ Total Score (mean change salmeterol −5.5 [SD13.1], placebo −1.1 [SD 11.6]; $P = 0.04$) and SGRQ Impacts (mean change salmeterol −6.4 [SD 17.0], placebo −0.1 [SD 15.8]; $P = 0.02$), but not for the other two subscales.[45]

The generally accepted MCID for a change in total SGRQ from baseline is 4.0 units, and a decrease in score indicates an improvement in HRQL.[67,68] The scoring of the SGRQ-C was adjusted to give scores equivalent to the SGRQ.[45] In the manual of the SGRQ-C, an MCID of 4.0 units is used for the within-group comparison, as well as the between-group comparison.[36] No MCID was reported for the domain scores.

Baseline Dyspnea Index and Transition Dyspnea Index

The Baseline Dyspnea Index (BDI) and Transition Dyspnea Index (TDI) are interviewer-administered, multidimensional indexes used to measure the severity of dyspnea. The BDI measures dyspnea at a single time-point and the TDI measures change from baseline dyspnea as measured by the BDI.[37,38] Both the BDI and the TDI consist of 24 items in three domains: Functional Impairment, Magnitude of Task, and Magnitude of Effort assessed in BDI, and the changes from baseline in Functional Impairment, Magnitude of Task, and Magnitude of Effort in TDI. Functional Impairment assesses the impact of breathlessness on the ability to carry out activities, Magnitude of Task determines the type of task causing breathlessness, and Magnitude of Effort determines the level of effort resulting in breathlessness.[69] At baseline, assessed by BDI, each domain is scored from grade 0 to grade 4, where grade 0 indicates the worst affected and grade 4 indicates no effect.[38] Three additional non-numeric items are available to capture reasons that a domain cannot

be scored.[38] The numeric domain scores are totalled to produce a BDI focal score ranging from 0 to 12, with a lower score indicating more severe dyspnea. Changes from baseline in dyspnea are assessed by TDI. Each domain in TDI is rated from −3 (major deterioration) to +3 (major improvement), with one non-numeric item available to capture further impairment for reasons other than dyspnea. The ratings for each of the three categories are totalled to form a total TDI score ranging from −9 to +9. A lower TDI score indicates more deterioration in the severity of dyspnea.

Test-retest reliability, internal consistency, and construct validity were assessed in 143 COPD patients recruited for a clinical trial, aged 40 to 86, with FEV_1 0.3 L to 3.53 L.[70] Construct validity and responsiveness were assessed in two identically designed clinical trials of treatment in patients with COPD involving 1,207 patients who were predominately male (approximately 75%) and had FEV_1 per cent-predicted 39.4% to 41.0% (depending on the treatment group).[70]

The test-retest reliability for the BDI was 0.76 (*r*), and the internal consistency alpha was 0.80. For both, a value of greater than 0.70 is considered reasonable evidence of reliability or internal consistency.[70]

Construct validity for the BDI was assessed in the first study by correlation against other dyspnea measures administered to the same patients. Correlation was high for the University of California, San Diego Shortness of Breath questionnaire (–0.70) and moderate for the American Thoracic Society Dyspnea Scale, the oxygen cost diagram, and the visual analogue scale for the past week (–0.50 to −0.59).[70] In the second study, construct validity for the BDI was assessed against measures of health status (SGRQ[69]), symptoms (dyspnoea diary[69]), and pulmonary function (FEV_1 and FVC[69]). Correlation between the BDI and the SGRQ total score was good, Pearson's correlation coefficient −0.64, with correlation between the BDI and SGRQ subscales of −0.35 (SGRQ Symptom) to −0.63 (SGRQ Activity). Correlation between dyspnoea diary score at baseline and respiratory function tests (FEV_1 and FVC) was lower, −0.34 and 0.25 to 0.31, respectively.[69]

Responsiveness of the TDI was assessed against changes in the SGRQ Total Score and subscales, dyspnoea diary, FEV_1, and FVC, and the physician global assessment. Changes in SGRQ Total Score was moderately correlated with TDI (Pearson's correlation coefficient of −0.40), with correlation between TDI and changes in SGRQ subscales of −0.32 to −0.33.[69] Correlation between BDI and changes in dyspnoea diary score, respiratory function, and Physician's global evaluation were low, −0.29 to 0.28.[69] When patients are classified as responders (at least a one-unit improvement) and non-responders, there was a statistically significant difference between groups in the use of rescue medication, and a clinically meaningful difference in SGRQ (four units).[69]

For the population in the clinical trials just described (75% male, moderate COPD), MCID was estimated by an anchor-based approach, relative to the Physician's global evaluation. A mean TDI score of one unit corresponded to clinically significant PGE changes of one to two points.[69]

Table 15: Summary of Validity of Outcomes Measures

Instrument	Type	Evidence of Validity	MCID	References
CAT	Eight items formatted as a semantic six-point differential scale yielding a combined score of 0 to 40, where higher scores represent worse health.	Yes	2 to 4 units	CAT[34,39]
EQ-5D-5L	A generic, self-reported measure of HRQL that contains the EQ-5D descriptive system and the EQ visual analogue scale (EQ-VAS). The descriptive system contains 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; each dimension has 5 levels. A single summary index can be generated for the descriptive system. The EQ-VAS has a score ranges from 0 to 100.	Yes	EQ-5D-5L utility score 0.037 to 0.109 EQ-VAS 6.5 to 10.1.	EQ-5D-5L[55]
EXACT-RS	A patient-reported outcome scale utilizing 11 respiratory symptom items, derived from the validated 14-item EXACT scale.	Yes	3.35[a]	EXACT-RS[58,59]
FEV_1	FEV_1 is the volume of air that, after a full inspiration, can be forcibly expired in one second.	Yes	0.10 L to 0.14 L	FEV_1[35]
SGRQ-C	SGRQ-C is a disease-specific measure of HRQL that consists of 14 questions and 40 items. The questionnaire is divided into three dimensions: symptoms, activity, and impacts of the disease. Scores for the Total Score and individual dimension ranges from 0 to 100, where 0 indicates no impairment and 100 indicates greatest impairment.	Yes	4 units	SGRQ-C[45,65]
TDI	TDI is used to measure change from baseline dyspnea as measured by the BDI and consists of 24 items measuring 3 categories: Functional Impairment, Magnitude of Task, and Magnitude of Effort. Items are rated in 7 grades ranging from −3 (major deterioration) to +3 (major improvement), where lower scores indicate more deterioration in the severity of dyspnea from baseline.	Yes	1 unit	TDI[37,69]

CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; EQ-5D-5L = EuroQol 5-Dimentions 5-Levels questionnaire; EXACT-RS = EXAcerbations of Chronic Pulmonary Disease Tool – Respiratory Symptoms; FEV_1 = forced expiratory volume in one second; SGRQ = St. George's Respiratory Questionnaire; TDI = Transitional Dyspnea Index; VAS = visual analogue scale.

[a] This minimal clinically important difference was estimated using a distribution-based method using data from a single study.[59]

Conclusion

CAT, EQ-5D-5L, EXACT-RS, FEV_1, and SGRQ-C are all considered to be valid outcomes measures for patients with COPD. Although EQ-5D-5L is classified as a generic health-related quality of life instrument, COPD-specific MCIDs have been determined. The available MCID's for CAT, EQ-5D-5L utility scale, EQ-5D-5L VAS, FEV_1, EXACT-RS, and SGRQ-C were −2 to −4 units, 0.037 to 0.109 units, 0.10 L to 0.14 L, 3.35 units and 4 units, respectively.

Appendix 6: Summary of Other Studies

Objective

To summarize the efficacy and safety results from Study 200109[32] and Study 200110.[33] Study 200109[32] and Study 200110[33] were considered to be supplemental studies for Health Canada's review of fluticasone furoate/umeclidinium/vilanterol.

Findings

Study Design

Study 200109[32] and Study 200110[33] were 12-week, double-blind, placebo-controlled, multi-centre, parallel-group studies designed to assess the efficacy and safety of umeclidinium (UMEC) 62.5 mg and 125 mg added to fluticasone furoate/vilanterol (FF/VI) 100/25 mg in patients with chronic obstructive pulmonary disease (COPD). In these trials, patients received UMEC 62.5 mcg and FF/VI 100/25 mcg, UMEC 125 mcg and FF/VI 100/25 mcg, or placebo and FF/VI 100/25 mcg. A summary of study characteristics is presented in Table 16.

Table 16: Details of Included Studies

		Study 200109	Study 200110
Designs and Populations	**Study Design**	RCT, DB	RCT, DB
	Locations	North America, Chile, Argentina, Romania	Germany, US, Korea, Czech Republic
	Randomized (N)	619	620
	Inclusion Criteria	Male and female patients ≥ 40 years of age who were current or former cigarette smokers (≥ 10 pack-years at Screening) diagnosed with COPD as defined by the ATS/ERS. Pre- and post-albuterol/salbutamol FEV_1/FVC ratio of < 0.70 and a pre- and post-albuterol/salbutamol FEV_1 of ≤ 70%. A dyspnea score of ≥ 2.Corrected QT interval < 480 msec; for patients with QRS ≥ 120 msec.	Male and female patients of ≥ 40 years of age who were current or former cigarette smokers (≥ 10 pack-years at Screening) diagnosed with COPD as defined by the ATS/ERS. Pre- and post-albuterol/salbutamol FEV_1/FVC ratio of < 0.70 and a pre- and post-albuterol/salbutamol FEV_1 of ≤ 70%. A dyspnea score of ≥ 2. Corrected QT interval < 480 msec; for patients with QRS ≥ 120 msec.
	Exclusion Criteria	Current diagnosis of asthma, other respiratory disorders, hospitalized for COPD or pneumonia within 12 weeks prior to visit 1, lung resection within 12 months of screening, or other clinically significant medical conditions.	Current diagnosis of asthma, other respiratory disorders, hospitalized for COPD or pneumonia within 12 weeks prior to visit 1, lung resection within 12 months of screening, or other clinically significant medical conditions.
Drugs	**Intervention**	UMEC 62.5 mcg + FF/VI 100/25 mcg UMEC 125 mcg + FF/VI 100/25 mcg	UMEC 62.5 mcg + FF/VI 100/25 mcg UMEC 125 mcg + FF/VI 100/25 mcg
	Comparator(s)	Placebo + FF/VI 100/25 mcg	Placebo + FF/VI 100/25 mcg
Duration	**Phase**		
	Run-in	4 weeks	4 weeks
	Double-blind	12 weeks	12 weeks
	Follow-up	1 week	1 week

		Study 200109	Study 200110
Outcomes	**Primary End Point**	Trough FEV_1 on day 85	Trough FEV_1 on day 85
	Other End Points	Weighted mean 0-6 hours FEV_1 post-dose on day 84	Weighted mean 0 to 6 hours FEV_1 post-dose on day 84
Notes	**Publications**	Siler et al., 2015[71]	Siler et al., 2015[71]

ATS = American Thoracic Society; COPD = chronic obstructive pulmonary disease; DB = double-blind; ERS = European respiratory Society; FEV_1 = forced expiratory volume in one second; FF = fluticasone furoate; FVC = forced vital capacity; RCT = randomized controlled trial; TDI = Transitional Dyspnea Index; UMEC = umeclidinium; VI = vilanterol.

Note: Two additional reports were included (CDR submission[30] and Health Canada's reviewers report[31]).

Source: CSRs for Study 200109[32] and Study 200110.[33]

Assessment

The assessment of efficacy and safety of UMEC 62.5 mg and 125 mg added to FF/VI 100/25 mg in patients with COPD were the primary objectives of Study 200109 and Study 200110. The primary end point was trough FEV_1 on day 85 (where trough FEV_1 was defined as the mean FEV_1 values obtained 23 and 24 hours after dosing on day 84). The secondary end point was the weighted mean zero to six hours FEV_1 post-dose on day 84 (calculated from the pre-dose FEV_1, and post-dose FEV_1 at 15 minutes, 30 minutes, one hour, three hours, and six hours).

The safety of UMEC 62.5 mg and 125 mg added to FF/VI 100/25 mg was assessed using the following end points:

- incidence of adverse events
- incidence of COPD exacerbation.

Results

Numerically more placebo patients had discontinued Study 200110 13% versus 5% and 7% of patients. Patients who discontinued Study 200109 were similar between groups. Patients experiencing lack of efficacy was the most common reason in both trials. Table 17 presents the detailed patient disposition for Study 2001009 and Study 200110.

Table 17: Patient Disposition

	Study 200109			Study 200110		
	Placebo + FF/VI 100/25	UMEC + FF/VI 62.5 + 100/25	UMEC + FF/VI 125 + 100/25	Placebo + FF/VI 100/25	UMEC + FF/VI 62.5 + 100/25	UMEC + FF/VI 125 + 100/25
Enrolled/ Pre-Screened, N	727			730		
Pre-Screen Failure, N	22			15		
Screened, N	705			715		
Screen Failure, N	70			85		
Randomized, N	619			620		
Discontinued, N (%)	15 (7)	11 (5)	18 (9)	26 (13)	11 (5)	7 (3)
Adverse event	5 (2)	2 (< 1)	4 (2)	9 (4)	7 (3)	2 (< 1)
Lack of efficacy	5 (2)	4 (2)	9 (4)	11 (5)	3 (1)	4 (2)
Lost to follow-up	0	1 (< 1)	0	2 (< 1)	0	1 (< 1)
Protocol deviation	1 (< 1)	2 (< 1)	0	0	0	0
Subject reached protocol-defined stopping criteria	0	0	1 (< 1)	0	0	0
Withdrew consent	4 (2)	2 (< 1)	4 (2)	4 (2)	1 (< 1)	0
Subject relocated	2 (< 1)	0	1 (< 1)	0	0	0
Frequency of visits	1 (< 1)	0	0	0	0	0
Other	1 (< 1)	2 (< 1)	0	4 (2)	1 (< 1)	0
ITT, N	206	206	207	206	206	207
PP, N	196	200	203	198	204	100

FF = fluticasone furoate; ITT = intention to treat; PP = per protocol; UMEC = umeclidinium; VI = vilanterol.

Source: CSRs for Study 200109[32] and Study 200110.[33]

Efficacy Outcomes

Table 18 presents results from the efficacy analysis for selected outcomes. The difference between placebo + FF/VI (100/25 mcg) and UMEC (62.5 mcg) + FF/VI (100/25 mcg) was 0.12 (95% CI, 0.093 to 0.154) in Study 200109, and 0.12 (95% CI, 0.091 to 0.152) in Study 200110. The difference between placebo + FF/VI (100/25 mcg) and UMEC (125 mcg) + FF/VI (100/25 mcg) was 0.13 (95% CI, 0.098 to 0.159) in Study 200109, and 0.11 (95% CI, 0.081 to 0.141) in Study 200110. The difference in the change from baseline trough FEV_1 was statistically significant ($P < 0.001$) across all trials at day 85. Similarly, using the zero to six-hour weighted mean FEV_1, the difference in the change from baseline trough FEV *1* was statistically significant ($P < 0.001$) across all trials at day 85.

Table 18: Efficacy Outcomes

	Study 200109			Study 200110		
	Placebo + FF/VI 100/25	UMEC + FF/VI 62.5 + 100/25	UMEC + FF/VI 125 + 100/25	Placebo + FF/VI 100/25	UMEC + FF/VI 62.5 + 100/25	UMEC + FF/VI 125 + 100/25
Pulmonary Function						
Baseline FEV_1 mean (SD)	1.24 (0.462)	1.20 (0.486)	1.26 (0.482)	1.39 (0.516)	1.37 (0.469)	1.40 (0.523)
LS mean change from baseline trough FEV_1[a] (SE)	–0.02 (0.011)	0.10 (0.011)	0.11 (0.011)	–0.03 (0.011)	0.09 (0.011)	0.08 (0.011)
Difference (95% CI)		0.12 (0.093 to 0.154)	0.13 (0.098 to 0.159)		0.12 (0.091 to 0.152)	0.11 (0.081 to 0.141)
P value		< 0.001	< 0.001		< 0.001	< 0.001
Pulmonary Function 0 to 6-hour weighted mean FEV_1						
LS mean change from baseline trough FEV_1[a] (SE)	0.03 (0.012)	0.19 (0.012)	0.18 (0.012)	0.02 (0.012)	0.16 (0.012)	0.15 (0.011)
Difference (95% CI)		0.15 (0.12 to 0.19)	0.14 (0.106 to 0.175)		0.15 (0.114 to 0.179)	0.14 (0.103 to 0.167)
P value		< 0.001	< 0.001		< 0.001	< 0.001

CI = confidence interval; FEV_1 = forced expiratory volume in one second; FF = fluticasone furoate; LS = least squares; SD = standard deviation; SE = standard error; UMEC = umeclidinium; VI = vilanterol.

Note: Baseline is the mean of the two assessments made at five minutes and 30 minutes pre-dose on day 1.

[a] Analysis performed using a repeated measures model with covariates of treatment group, baseline (mean of the two assessments made at five minutes and 30 minutes pre-dose on day 1), smoking status, day, day by baseline, and day by treatment interactions.

Source: CSRs for Study 200109[32] and Study 200110.[33]

Safety Outcomes

Table 19 presents harms data for patients in Study 200109 and Study 200110. Adverse events were reported in 36% and 33% of patients in the UMEC (62.5 mcg) + FF/VI (100/25 mcg) group; 39% and 30% of patients in the UMEC (125 mcg) + FF/VI (100/25 mcg); 35% and 39% of patients in the placebo + FF/VI (100/25 mcg) group for Study 200109 and Study 200110 at week 12, respectively.

Severe adverse events were reported in less than 1% and 4% of patients in the UMEC (62.5 mcg) + FF/VI (100/25 mcg) group; 3% and 1% of patients in the UMEC (125 mcg) + FF/VI (100/25 mcg); 2% and 5% of patients in the placebo + FF/VI (100/25 mcg) group for Study 200109 and Study 200110 at week 12, respectively. Severe adverse events due to COPD exacerbation were reported in zero to 2% of patients across treatment groups in the trials. Withdrawals due to adverse events ranged from less than 1% to 4 % of patients across treatment groups in the trials. One death occurred in the placebo group in Study 200109. Five deaths occurred in Study 200110, with four in the placebo group and one in the UMEC (62.5 mcg) + FF/VI (100/25 mcg) group.

Table 19: Harms

	Study 200109			Study 200110		
	Placebo + FF/VI 100/25	UMEC + FF/VI 62.5 + 100/25	UMEC + FF/VI 125 + 100/25	Placebo + FF/VI 100/25	UMEC + FF/VI 62.5 + 100/25	UMEC + FF/VI 125 + 100/25
AEs						
Patients with > 0 AEs, N (%)	72 (35)	75 (36)	80 (39)	81 (39)	67 (33)	62 (30)
SAEs						
Patients with > 0 SAEs, N (%)	5 (2)	2 (< 1)	7 (3)	11 (5)	8 (4)	3 (1)
COPD exacerbation	1 (< 1)	0	4 (2)	3 (1)	3 (1)	1 (< 1)
WDAEs						
Patients with > 0 WDAEs, N (%)	5 (2)	3 (1)	6 (3)	9 (4)	7 (3)	2 (< 1)
Deaths						
Number of deaths, N (%)	1 (< 1)	0	0	4 (2)	1 (< 1)	0

AE = adverse event; COPD = chronic obstructive pulmonary disease; FF = fluticasone furoate; SAE = serious adverse event; UMEC = umeclidinium; VI = vilanterol, WDAE = withdrawal due to adverse event.

Source: CSRs for Study 200109[32] and Study 200110.[33]

Limitations

The main limitations for Study 200109 and Study 200110 relate to the length of the trials and the implication for the interpretation of the efficacy and harms data. Both trials were 12 weeks in duration; this limits the outcomes that can be assessed (i.e., limited to FEV_1-related outcomes). Relevant outcomes related to exacerbations, health care resource utilization, mortality (all-cause and due to COPD) were not assessed in these trials. It is also unclear the 12-week duration would be sufficient to assess harms data pertaining to adverse events of special interest (i.e., cardiovascular, pneumonia, corticosteroid adverse events, anticholinergic adverse events).

Another limitation for Study 200109 and Study 200110 relate to the exclusion of patients with a current diagnosis of asthma. This criterion was not based on spirometry. Generally asthma is characterized by a number of criteria including spirometry showing reversible airway obstruction (reduced FEV_1/FVC of [less than 0.75 to 0.8] and increase in FEV_1 after a bronchodilator or after a course of controller therapy [≥ 12% and a minimum of ≥ to 200 mL]).[72] This presents an issue, as it is possible for undiagnosed patients that meet the asthma criteria to be included in the study population. This limits the generalizability of results, potentially reducing the applicability to the targeted COPD population.

Discussion

Selected efficacy results focused on pulmonary function. Results for FEV_1 differences and time-weighted FEV_1 differences showed a statistically significant ($P < 0.001$) improvement across treatment groups compared with placebo plus FF/VI (100/25 mcg) in both trials, thereby supporting the use of triple therapy in patients with COPD.

Safety results were similar across comparison groups in both trials for adverse events, severe adverse events, and withdrawals due to adverse events. One death occurred in the placebo group in Study 200109. Five deaths occurred in Study 200110, with four in the placebo group and one in the UMEC (62.5 mcg) + FF/VI (100/25 mcg) group.

Summary

The efficacy and safety of adding UMEC (62.5 mg and 125 mg) to FF/VI provides significant improvements in pulmonary function and similar harms compared with placebo and FF/VI. One death occurred in the placebo group in Study 200109 and five deaths occurred in Study 200110. Limitations to both trials included a short trial duration and minimal efficacy assessments.

Appendix 7: Summary of FULFIL Extension Subset

The FULFIL trial included a subset of 430 patients in an extension of the trial where patients remained in the trial for a total of 52 weeks. These patients were the first to be enrolled and consent to the extension. Patients remained in the treatment group they were randomized to at the initiation of the FULFIL trial. Baseline characteristics and demographics were similar between treatment arms (Table 20).

Table 20: Summary of Baseline Characteristics for FULFIL Extension Study

	FULFIL Extension Subset	
	FF/UMEC/VI 100/62.5/25 N = 210	BUD/FOR 400/12 N = 220
Male, n (%)	157 (75)	162 (74)
Age, years mean (SD)	63.7 (7.76)	63.3 (8.43)
Smoking status, n (%)		
Current smoker	95 (45)	97 (44)
Former smoker	115 (55)	123 (56)
GOLD grade, n (%)		
1 (mild)	0	1 (< 1)
2 (moderate)	76 (37)	74 (34)
3 (severe)	108 (52)	108 (49)
4 (very severe)	24 (12)	36 (16)
Post-bronchodilator FEV_1/FVC ratio		
Mean (SD)	0.47 (0.107)	0.45 (0.110)
Exacerbation history[a]		
< 2 moderate and no severe	90 (43)	103 (47)
≥ 2 moderate or ≥ 1 severe	120 (57)	117 (53)
CAT score, mean (SD)	19.3 (4.71)	19.0 (4.68)

CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disorder; FF = fluticasone furoate; GOLD = Global initiative for chronic Obstructive Lung Disease; SD = standard deviation; UMEC = umeclidinium; VI = vilanterol.

[a] Moderate/severe exacerbations in the past year. Moderate exacerbation: required treatment with oral/systemic corticosteroids and/or antibiotics (not involving hospitalization); Severe exacerbation: required hospitalization.

[b]Reversible is an increase in FEV_1 of ≥ 12% and ≥ 200 mL following administration of salbutamol. Source: CSRs for FULFIL.[7]

Efficacy Outcomes

Table 21 presents efficacy results for patients in the FULFIL extension subset. Pulmonary function was assessed using the FEV_1. The change from baseline in trough FEV_1 was evaluated as a secondary outcome (at week 52) in IMPACT. In the extension subset, the difference in least squares change from baseline in trough FEV_1 at 52 weeks was 0.18 L (95% CI, 0.13 L to 0.23 L).

The annual rate of on-treatment moderate/severe exacerbations was assessed as a secondary outcome and the time to first moderate or severe COPD exacerbation was assessed as an “other” outcome in FULFIL. In the extension subset, the difference in rate of on-treatment moderate/severe exacerbations was determined to have a rate ratio of 0.54 (95% CI, 0.37 to 0.85). The ratio for time to first on-treatment moderate or severe

exacerbation showed a significant reduction for FF/UMEC/VI compared with budesonide at week 52 (hazard ratio = 0.54, 95% confidence interval [CI], 0.35 to 0.83).

Health-related quality of life was assessed using the SGRQ. In the extension subset, the difference in least squares change from baseline in SGRQ total score at 52 weeks was −2.7 units (95% CI, −5.5 units to 0.2 units).

FULFIL evaluated COP- related respiratory symptoms using the EXAcerbations of Chronic Pulmonary Disease Tool – Respiratory Symptoms (EXACT-RS). In the extension subset, the treatment difference between week 49 and 52 was −1.42 units (95% CI, −2.45 units to −0.39 units)

FULFIL assessed the health status and disease impact using the COPD assessment test, where the difference in least squares mean change was −0.4 units (95% CI, −0.8 units to −0.1 units) for the extension subset.

FULFIL assessed the use of rescue medications in the extension subset, where reduction in the mean number of occasions of rescue medication was determined to be −0.2 occasions (95% CI, −0.4 occasions to 0.0 occasions).

Table 21: Efficacy Outcomes for FULFIL Extension Study

	FULFIL Extension Subset	
	FF/UMEC/VI 100/62.5/25 N = 210	BUD/FOR 400/12 N = 220
Pulmonary Function		
Baseline FEV_1 Mean (SD)	1.33 (0.504)	1.28 (0.482)
n with analyzable data at Week 52	183	171
LS mean change from baseline trough FEV_1[a] (SE)	0.13 (0.017)	–0.05 (0.017)
Difference (95% CI)	0.18 (0.13 to 0.23)	
Adjusted *P* value[b]	< 0.001	
Moderate/Severe Exacerbations		
n	210	219
Mean annual exacerbation rate[c]	0.20	0.36
Ratio (95% CI)	0.56 (0.37 to 0.85)	
P value	0.006	
Time to first on-treatment moderate or severe exacerbation hazard ratio (95% CI)	0.54 (0.36 to 0.83)	
P value	0.005	
SGRQ		
n with analyzable data at week 52	182	174
Mean (SD)	53.0 (16.14)	50.8 (15.49)
LS mean change from baseline SGRQ Total Score[a] (SE)	−4.6 (1.01)	−1.9 (1.03)
Difference (95% CI)	−2.7 (−5.5 to 0.2)	
Adjusted *P* value[b]	NA	
P value	0.065	
SGRQ Responder,[d] N (%)	91 (44)	73 (33)

	FULFIL Extension Subset	
	FF/UMEC/VI 100/62.5/25 N = 210	BUD/FOR 400/12 N = 220
Odds ratio[e,f] (95% CI)	1.50 (1.01 to 2.24)	
P value	0.046	
CAT		
Baseline CAT mean (SD)	18.1 (6.29)	17.7 (5.93)
n with analyzable data at week 52	182	172
LS mean change (SE)	−1.7 (0.41)	−1.0 (0.42)
Difference (95% CI)	−0.8 (−1.9 to 0.4)	
P value	0.181	
EXACT-RS		
Baseline mean (SD)	13.5 (5.44)	13.0 (15.58)
n	179	171
EXACT-RS treatment difference between weeks 49 to 52 (95% CI)	–1.42 (–2.45 to −0.39)	
P value	0.007	
Baseline Dyspnea Index Focal Score		
Mean (SD)	5.9 (1.58)	5.5 (1.70)
Transition Dyspnea Index Focal Score		
n analyzable data at week 52	182	173
LS mean (SE)	1.74 (0.221)	1.39 (0.226)
Difference (95% CI)	0.34 (−0.28 to 0.97)	
P value	0.279	
Rescue Medication		
Baseline mean use per day (SD)	1.6 (1.95)	1.5 (1.87)
n	205	213
LS mean change (SE)	−0.1 (0.08)	0.1 (0.08)
Difference (95% CI)	-0.2 (−0.4 to 0.0)	
P value	0.019	

BUD = budesonide; CAT = COPD assessment test; CI = confidence interval; COPD = chronic obstructive pulmonary disease; EXACT-RS = EXAcerbations of Chronic Pulmonary Disease Tool – Respiratory Symptoms; FEV_1 = forced expiratory volume in one second; FF = fluticasone furoate; FOR = formoterol fumarate; LS = least squares; SD = standard deviation; SE = standard error; SGRQ = St. George's Respiratory Questionnaire; UMEC = umeclidinium; VI = vilanterol.

[a] Analysis performed using a repeated measures model with covariates of treatment group, smoking status (screening), geographical region, visit, baseline, and baseline-by-visit and treatment-by-visit interactions.

[b] Adjusted for multiplicity. The adjusted *P* value at week 24 was compared against a reference level of 0.05 in order to infer statistical significance.

[c] Analysis performed using a generalized linear model assuming a negative binomial distribution and covariates of treatment group, exacerbation history (0, 1, ≥ 2 moderate/severe), smoking status (screening), geographical region, and post-bronchodilator per cent-predicted FEV_1 (day 1).

[d] Response was defined as an SGRQ Total Score of ≥ 4 units below baseline. Non-response was defined as a SGRQ Total Score of < 4 units below baseline or data missing for the analysis.

[e] Ratio of odds of response versus non-response.

[f] Analysis performed using a generalized linear mixed model with a logit link function and covariates of treatment group, smoking status (screening), geographical region visit, baseline, and baseline-by-visit and treatment-by-visit interactions.

Source: CSR for FULFIL.[7]

Safety Outcomes

Table 22 presents harms data for patients in the FULFIL extension subset. Adverse events were reported in 48% and 56% of patients in the FF/UMEC/VI) and the budesonide/formoterol fumarate (BUD/FOR) arms, respectively.

Severe adverse events were reported in 10% and 13% of patients in the FF/VI/UMEC and the BUD/FOR arms, respectively. Withdrawals due to adverse events were reported in 5% and 4% of patients in the FF/VI/UMEC and the BUD/FOR arms, respectively. Two deaths occurred in the FF/UMEC/VI arm and one death occurred in the BUD/FOR arm. Anticholinergic syndrome was reported in more patients in the BUD/FOR arm (6%) than the FF/UMEC/VI arm (2%).

Table 22: Harms for FULFIL Extension Study

	FULFIL Extension Subset	
	FF/UMEC/VI 100/62.5/25 N = 210	BUD/FOR 400/12 N = 220
AEs		
Subjects with > 0 AEs, N (%)	100 (47.6)	122 (55.5)
SAEs		
Subjects with > 0 SAEs, N (%)	21 (10.0)	28 (12.7)
WDAEs		
WDAEs, N (%)	10 (4.8)	9 (4.1)
Deaths		
Number of deaths, N (%)	2 (1.0)	1 (0.5)
Notable Harms, N (%)		
Anticholinergic syndrome	4 (1.9)	12 (5.5)
CV effects	18 (8.6)	22 (10.0)
Local steroid effects	8 (3.8)	7 (3.2)
Pneumonia	4 (1.9)	4 (1.8)

AE = adverse event; BUD = budesonide; CV = cardiovascular; FF = fluticasone furoate; FOR = formoterol fumarate; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Source: CSRs for FULFIL.[7]

Appendix 8: Summary of Indirect Comparisons

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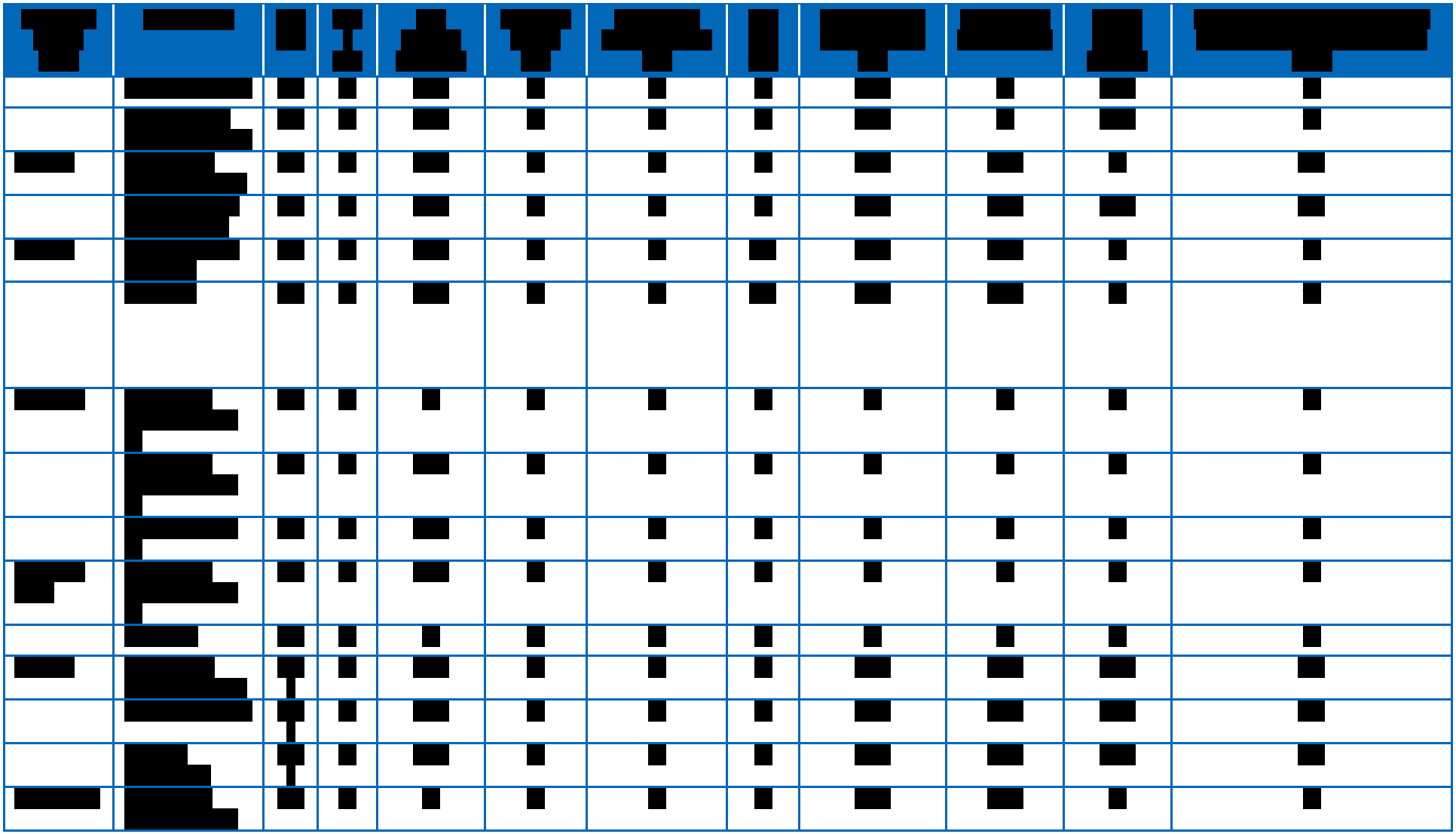

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