Common Drug Review
Clinical Review Report

November 2016

Drug	fluticasone furoate/vilanterol (Breo Ellipta)
Indication	Long-term once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, and to reduce exacerbations of COPD in patients with a history of exacerbations.
Listing request	For the maintenance treatment of moderate to severe COPD, to reduce exacerbations.
Manufacturer	GlaxoSmithKline

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

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ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
CDR	CADTH Common Drug Review
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRQ-SAS	Chronic Respiratory Questionnaire Self-Administered Standardized
CSR	clinical study report
DB	double-blind
DBRCT	double-blind randomized controlled trial
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in one second
FF/V	fluticasone furoate /vilanterol
FM	formoterol
FP/S	fluticasone propionate /salmeterol
FP/V	fluticasone propionate plus vilanterol
FVC	forced vital capacity
HR	hazard ratio
HRQoL	health-related quality of life
IC	inspiratory capacity
ICS	inhaled corticosteroid
ICU	intensive care unit
ITT	Intention-to-treat
IVRS	interactive voice response system
LAAC	long-acting anticholinergic
LABA	long-acting beta-agonist
LOCF	last observation carried forward
LS	least squares
MCID	minimal clinically important difference
mMRC	Modified Medical Research Council Dyspnea Scale
SAAC	short-acting anticholinergic
SABA	short-acting beta-agonist
SAE	serious adverse event
SD	standard deviation
SGRQ	St. George's Respiratory Questionnaire
SGRQ-C	St. George's Respiratory Questionnaire for COPD

EXECUTIVE SUMMARY

Introduction

Chronic obstructive pulmonary disease (COPD) is a respiratory disorder characterized by progressive, partially reversible airway obstruction and lung hyperinflation, systemic manifestations, and increasing frequency and severity of exacerbations.[1, 2] There is overlap of COPD subtypes, with many individuals presenting with features of both chronic bronchitis and emphysema, as well as asthma, which differs fundamentally from COPD.[2] According to a 2009 Statistics Canada report, COPD affects 4% of the Canadian population aged 35 years or older.[3] The goals of COPD management are to prevent disease progression, reduce frequency, and severity of exacerbations, alleviate symptoms, improve exercise tolerance and daily activity, treat exacerbations and complications, improve health status, and reduce mortality.[1]

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.[2] Bronchodilators form the mainstay of pharmacotherapy for COPD [2] and include short-acting beta-agonists (SABAs) and antimuscarinic drugs (salbutamol and antimuscarinics [SAMAs]). Long-acting beta-agonists (LABAs) or antimuscarinic (long-acting anticholinergic [LAAC]) drugs as well as combinations of fixed-dose LABAs and inhaled corticosteroids (LABA plus ICS) are the most commonly used treatments for COPD in Canada. Antimuscarinic and beta-agonist drugs are often used in combination for maximal improvement in dyspnea and function. Inhaled steroids may not be useful for mild disease; however, they may have more of a role in the management of moderate to severe COPD, or in those with persistent symptoms.[4-6] There may also be a subpopulation of COPD patients who have concomitant asthma or airway eosinophilia, where ICS use may be beneficial.[7-9] Inhaled medications are most commonly delivered as pressurized metered-dose inhalers and dry powder inhalers.

Indication under review
Breo Ellipta (fluticasone furoate/vilanterol) is indicated for the long-term once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, and to reduce exacerbations of COPD in patients with a history of exacerbations.
Listing criteria requested by sponsor
For the maintenance treatment of moderate to severe COPD, to reduce exacerbations.

The objective of this review was to perform a systematic review of the beneficial and harmful effects of fluticasone furoate/vilanterol (FF/V; Breo Ellipta) for the treatment of patients with COPD, including chronic bronchitis and/or emphysema.

Results and Interpretation

Included Studies

Ten double-blind (DB) randomized controlled trials (RCTs) met the inclusion criteria for this systematic review. Five were active-controlled, with fluticasone propionate + salmeterol (Advair) as comparator in four studies (studies 2352, 3107, 3109, and 6974), and tiotropium (study 5805) as the comparator in the other. One of the fluticasone propionate + salmeterol studies used the higher 500/50 mcg dose (study 3107), while the others all used fluticasone propionate + salmeterol 250/50. Another three studies had a placebo control; two of these studies had placebo and components of fluticasone furoate + vilanterol, fluticasone furoate, and vilanterol, as groups (studies 2206 and 2207); while the other was a crossover design, with three different doses of fluticasone furoate + vilanterol and placebo as groups (study 946). Finally, two studies compared fluticasone furoate + vilanterol to vilanterol (study 2871 and 2970). The duration of treatment across the studies ranged from four weeks in the crossover study, to 12 weeks in the active-controlled studies, to 24 weeks in the placebo-controlled studies, and 52 weeks in the vilanterol-controlled studies.

Key critical appraisal issues include the short duration of the 12-week active-comparator studies versus fluticasone propionate + salmeterol and tiotropium, particularly for assessing important harms such as pneumonia. External validity issues include the relatively young population (minimum age of 40 years) and the high proportion of patients exhibiting bronchodilator reversibility, suggestive of asthma.

Efficacy

a) Mortality

Active-Controlled

In study 6974, there was one death in a fluticasone furoate + vilanterol patient and three deaths with fluticasone propionate + salmeterol. In the fluticasone propionate plus salmeterol-controlled studies, there was only one death per study. In study 5805, there were two deaths with tiotropium and none with fluticasone furoate plus vilanterol. Across the studies, the most common reason was cardiorespiratory arrest. There were no COPD-related deaths in the active-controlled studies.

Placebo-Controlled

There were few deaths in studies 2206 and 2207. One patient died on treatment in each of the fluticasone furoate plus vilanterol and placebo groups. There were no deaths with fluticasone furoate, and three with vilanterol. No patients died due to COPD.

Vilanterol-Controlled

In the vilanterol-controlled studies, there were eight deaths with fluticasone furoate plus vilanterol and eight deaths with vilanterol. There were two deaths due to COPD with each of fluticasone furoate plus vilanterol and vilanterol.

b) Quality of Life

Active-Controlled

Quality of life was assessed using the St. George's Respiratory Questionnaire (SGRQ) in studies 3107 and 5805. A decrease in score represents improvement. There was no difference in change from baseline in total score when fluticasone furoate plus vilanterol was compared to fluticasone propionate plus salmeterol or to tiotropium. [redacted]

[redacted]

Placebo-Controlled

Quality of life was assessed using the CRQ-SAS instrument in the placebo-controlled studies (2206 and 2207). The CRQ-SAS dyspnea subscale was statistically significantly improved from baseline for fluticasone furoate plus vilanterol versus placebo in both study 2206 (mean between-group difference [95% confidence interval (CI)]: 0.30 [0.06 to 0.54], *P* = 0.014) and study 2207 (mean between-group difference [95% CI]: 0.24 [0.02 to 0.46], *P* = 0.029). The individual components of fluticasone furoate plus vilanterol, fluticasone furoate, and vilanterol did not improve scores versus placebo. Similarly, the CRQ-SAS total score was statistically significantly improved for fluticasone furoate plus vilanterol versus placebo in both study 2206 (mean between-group difference [95% CI]: 0.25 [0.07 to 0.42], *P* = 0.005) and study 2207 (mean between-group difference [95% CI]: 0.21 [0.04 to 0.38], *P* = 0.015), and the individual components of fluticasone furoate plus vilanterol failed to demonstrate improvement versus placebo.

Quality of life was not reported in the vilanterol-controlled studies or in the crossover study.

c) Forced Expiratory Volume in One Second

Active-Controlled

The change from baseline in weighted-mean forced expiratory volume in one second (FEV_1) over 0 to 24 hours was the primary outcome of all the active-controlled studies. For FEV_1 weighted mean over 0 to 24 hours, there was no statistically significant difference in least squares (LS) mean change from baseline to 12 weeks between fluticasone furoate plus vilanterol and fluticasone propionate plus salmeterol in three of four studies. The exception was study 3109, where the fluticasone furoate plus vilanterol group had an increase of 0.174 versus 0.094 L with fluticasone propionate plus salmeterol ($P < 0.001$). There was no statistically significant difference for this outcome for change from baseline at 12 weeks when fluticasone furoate plus vilanterol was compared with tiotropium in study 5805.

In the two studies (3107 and 6974) reporting LS mean change from baseline to 12 weeks for trough FEV_1, no statistically significantly difference between fluticasone furoate plus vilanterol and fluticasone propionate plus salmeterol, or between fluticasone furoate plus vilanterol and tiotropium was found.

[redacted]

Placebo-Controlled
In studies 2206 and 2207, both the mean change from baseline to 24 weeks for FEV_1 (0 to 4 hours) and for trough FEV_1 were statistically significantly improved versus placebo. These were the co-primary outcomes of these studies.

For trough FEV_1, the between-group difference in mean change from baseline (95% CI) was 0.115 L ([0.060 to 0.169], $P < 0.001$) in study 2206 and 0.145 L ([0.095 to 0.196], $P < 0.001$) in study 2207. Looking at individual components of fluticasone furoate plus vilanterol, improvements from baseline were greater for vilanterol (study 2206: mean ± standard deviation [SD] change from baseline of 0.111 ± 0.256 L; study 2207: 0.109 ± 0.254 L) than for fluticasone furoate (study 2206: 0.089 ± 0.284 L; study 2207: 0.034 ± 0.241 L).

For FEV_1 (0 to 4 hours), in study 2206 the between-group difference in mean change from baseline (95% CI) was 0.173 ([0.123 to 0.224], $P < 0.001$) for fluticasone furoate plus vilanterol versus placebo and in study 2207 it was 0.214 ([0.161 to 0.266], $P < 0.001$) for fluticasone furoate plus vilanterol versus placebo.

Trough FEV_1 responses were available by subgroups. Response by baseline reversibility status was only reported for study 2206, and the direction of response was similar between patients exhibiting baseline reversibility and those not. No interaction *P* values were reported. Baseline smoking status (current or former smokers) also did not appear to affect FEV_1 trough responses, although this was reported only in study 2207.

Vilanterol-Controlled
FEV_1 (0 to 4 hours) or FEV_1 (0 to 24 hours) were not reported in either study 2871 or 2970. The mean change from baseline to 52 weeks in trough FEV_1 was statistically significantly improved for fluticasone furoate plus vilanterol versus vilanterol alone in study 2871 (between-group difference of mean [95% CI] change from baseline: 0.058 L [0.027 to 0.090], $P < 0.001$), but not in study 2970.

Crossover
LS mean change from baseline to 4 weeks for FEV_1 (0 to 24 hours) and trough FEV_1 were both statistically significantly improved for fluticasone furoate plus vilanterol versus placebo in study 946. For FEV_1 (0 to 24 hours), the between-group difference in LS mean change from baseline (95% CI) was 0.220 ([0.165 to 0.275], $P < 0.001$) and for trough FEV_1 it was 0.177 ([0.097 to 0.257], $P < 0.001$).

d) Symptoms
Active-Controlled
[redacted]

Placebo-Controlled
The mean improvement in CRQ-SAS dyspnea and total scores was statistically greater for fluticasone furoate plus vilanterol than for placebo after 24 weeks in each of studies 2206 and 2207. Further details are provided under the quality-of-life data.

Other symptoms scores assessed were based on diaries for cough, sputum, and breathlessness for weeks 1 to 24 of treatment, and each of these were statistically significantly improved for fluticasone furoate plus vilanterol versus placebo for both studies 2206 and 2207. [redacted]

Vilanterol-Controlled
Dyspnea scores (by interactive voice response system [IVRS] diary) for weeks 1 to 52 were statistically significantly improved for fluticasone furoate plus vilanterol versus vilanterol in each of studies 2871 (LS mean, between-group difference [95% CI]: –0.08 [–0.14 to –0.01], *P* = 0.019) and 2970 (–0.11 [–0.17 to –0.05], *P* < 0.01). These studies also reported the proportion of 24-hour periods without increased sputum; however, statistical analysis was not presented.

Crossover
Symptoms were not reported in this study.

e) Exacerbations

Active-Controlled
There were a similar number of exacerbations between fluticasone furoate plus vilanterol and fluticasone propionate plus salmeterol groups in the two studies reporting (study 3107: six versus seven exacerbations, respectively, [redacted] although these were not reported as an efficacy outcome, but as a safety outcome. No statistical analyses were provided in any of these studies. All of the exacerbations were reported as having resolved, and the majority were resolved using oral steroids. [redacted] There was no obvious pattern of exacerbations leading to hospitalization, and the numbers were too small to draw any conclusions.

Placebo-Controlled
Exacerbations were reported in both studies 2206 and 2207. The proportion of patients with an exacerbation in study 2206 was 9% of fluticasone furoate plus vilanterol-treated patients and 10% with placebo, and in study 2207, the proportions were 6% and 10% respectively. No statistical analyses were provided.

Vilanterol-Controlled
The annualized rate of moderate/severe exacerbations was the primary outcome for studies 2871 and 2970. In both studies 2871 and 2970, the annualized rate of moderate/severe exacerbations was statistically significantly lower for fluticasone furoate plus vilanterol versus vilanterol (study 2871, LS mean of 0.70 versus 1.05, *P* < 0.001; study 2970, LS mean of 0.92 versus 1.14, *P* = 0.024). The same was true for the annualized rate of all exacerbations, which in study 2871 was 0.92 for fluticasone furoate plus vilanterol, versus 1.37 for vilanterol (*P* < 0.001), and in study 2970 was 1.25 versus 1.55 (*P* = 0.034), respectively. The time to first moderate/severe exacerbation was also reported as a hazard ratio (HR) for each study, and these were statistically improved for fluticasone furoate plus vilanterol versus vilanterol in study 2871 (HR [95% CI]: 0.72 [0.59 to 0.89]) and study 2970 (0.80 [0.66 to 0.99], *P* = 0.036).

Exacerbations were further broken down by severity (moderate versus severe) and characterized by utilization of health care resources (resulting in home visit, physician visit, etc.), although no statistical analysis was provided. However, in both studies there were numerically fewer moderate exacerbations with fluticasone furoate plus vilanterol versus vilanterol (study 2871: 71 versus 81; study 2970: 265 versus 346). In study 2871, there were numerically fewer severe exacerbations with fluticasone furoate plus vilanterol versus vilanterol (36 versus 46), but there was no difference in study 2970 (41 versus 39).

Subgroup analyses were also presented by baseline reversibility to bronchodilators (study 2970) and smoking status (study 2871) for the primary outcome, with no clear impact of baseline characteristics on the annual rate of moderate/severe exacerbations. However, no interaction *P* values were reported.

Crossover
Exacerbations were not reported in study 946.

f) Resource Use

Active-Controlled

[redacted] A majority of patients received oral steroids to resolve their exacerbation, and many were treated with antibiotics (between 50% and 100% of exacerbations received antibiotics).

Placebo-Controlled
In patients with severe exacerbations, there were a similar number of in-patient hospital days on the ward for fluticasone furoate plus vilanterol versus placebo (33 each) in study 2871. There were 20 ward hospital days with fluticasone furoate and 45 days with vilanterol monotherapy. No statistical analyses were provided. [redacted]

Vilanterol-Controlled

[redacted]

Crossover
No hospitalization data were reported for study 946.

g) Harms

The proportion of patients with an adverse event (AE) differed across the active-controlled studies, ranging between 20% and 36%, and the incidence increased in the 24-week and the 52-week studies. Pneumonia was an infrequent AE (less than 1% of patients), and there was no clear difference in incidence of pneumonia between groups in any of the active-controlled studies. In the placebo-

controlled studies, there were six fluticasone furoate plus vilanterol-treated patients with pneumonia, compared with three placebo patients. In the 52-week vilanterol-controlled studies, there appeared to be a numerical increase in risk for pneumonia with fluticasone furoate plus vilanterol versus vilanterol (51 patients versus 27 patients, respectively, across the two studies). Headache was the most common AE across groups and studies.

Serious AEs were infrequent, ranging between 1% and 5% across the 12-week active-controlled studies. In the placebo-controlled studies, the proportion of patients with a serious AE was higher, ranging between 3% and 8%. In the 52-week vilanterol-controlled studies, the proportion of patients with serious AEs ranged between 14% and 17%. COPD was the most common event.

Withdrawals due to AEs ranged between less than 1% and 4% in the 12-week active-controlled studies, 6% and 12% in the placebo-controlled studies, and 5% to 9% in the vilanterol-controlled studies.

Other Considerations

According to the Health Canada reviewer's report, fluticasone furoate plus vilanterol is the first drug to be approved in Canada for the reduction of COPD exacerbations.

[redacted]

Neither fluticasone furoate nor vilanterol are approved as separate inhalers in Canada.

Pharmacoeconomic Summary

At the submitted confidential price of [redacted] per 100/25 mcg inhaler ([redacted] daily), compared with other ICS/LABA combinations already reimbursed in some jurisdictions for the treatment of COPD, fluticasone furoate plus vilanterol is less expensive than fluticasone propionate plus salmeterol (FP/S) (250/50 to 500/50 mcg twice daily, $3.25 to $4.61 daily) and [redacted] BUD/FM (budesonide/formoterol) (400/12 mcg twice daily, $2.76 daily). If listed, and assuming equivalent efficacy and safety assumptions are valid, fluticasone furoate plus vilanterol would not result in additional costs for patients who would otherwise be prescribed an ICS/LABA combination, but is more expensive than monotherapy with the available LAACs ($1.77 to $2.35 daily), another recommended treatment option for patients with more moderate COPD. For the cost of fluticasone furoate plus vilanterol to be equivalent with LAAC products, the price of fluticasone furoate plus vilanterol would need to be reduced by [redacted].

Conclusions

Results from five active-comparator trials suggest similar efficacy with respect to improvements in FEV_1 and frequency of exacerbations for fluticasone furoate plus vilanterol versus fluticasone propionate plus salmeterol, and similar efficacy for FEV_1 versus tiotropium, over the course of 12 weeks. The study that compared fluticasone furoate plus vilanterol versus tiotropium did not report exacerbations as an efficacy outcome. Fluticasone furoate plus vilanterol reduced exacerbations over one year versus vilanterol alone, although there were inconsistent results for improvements in FEV_1 when fluticasone furoate plus vilanterol was compared with vilanterol monotherapy. Harms, including pneumonia, were similar between fluticasone furoate/vilanterol and either fluticasone propionate plus salmeterol or tiotropium. In the 52-week studies, the incidence of pneumonia was numerically higher with fluticasone furoate plus vilanterol than with vilanterol monotherapy. Studies with longer duration of treatment would be needed to determine whether there are differences in the risk of pneumonia between fluticasone furoate plus vilanterol and other active comparators.

TABLE 1: SUMMARY OF RESULTS: STUDIES VERSUS FLUTICASONE PROPIONATE/SALMETEROL

	Study 3107		Study 6974		Study 3109		Study 2352	
	FF/V 100/25 N = 266	FP/S 500/50 N = 262	FF/V 100/25 N = 260	FP/S 250/50 N = 259	FF/V 100/25 N = 259	FP/S 250/50 N = 252	FF/V 100/25 N = 259	FP/S 250/50 N = 252
FEV_1, 0 to 24-Hour Weighted Mean								
LS mean change from baseline (SE) day 84, L	0.130 (0.22 2)	0.108 (0.221)	0.168 (0.012)	0.142 (0.012)	0.174 (0.015)	0.094 (0.016)	0.142 (0.018)	0.114 (0.018)
LS MD (95% CI)	0.022 (–0.018 to 0.063)		0.025 (–0.008 to 0.059)		0.080 (0.037 to 0.124)		0.029 [–0.022 to 0.080)	
P value	*P* = 0.282		*P* = 0.137		*P* < 0.001		*P* = 0.267	
Trough FEV_1								
Weighted mean (SD) day 85, L	0.111 (0.241)	0.088 (0.241)	0.151 (0.0126)	0.121 (0.0125)	NR	NR	NR	NR
LS MD (95% CI)	0.023 (–0.020 to –0.066)		0.030 (–0.005 to 0.065)		NR	NR	NR	NR
P value	NR		NR					
SGRQ Total Score								
Week 12, mean (SD) change	–4.3 (11.8)	–3.0 (11.8)	NR	NR	NR	NR	NR	NR
LS MD (95% CI)	–1.3 [–3.5 to 0.8]		NR	NR	NR	NR	NR	NR
P value	NR							
Deaths (All-Cause)								
On treatment, n (%)	1	0	1	3	0	1	1	0
Deaths, COPD								
On treatment, n (%)	0	0	0	0	0	0	0	0
Exacerbations								
Total	6	7	[redacted]	[redacted]	NR	NR	NR	NR
Withdrawals								
Total, n (%)	23 (9)	16 (6)	46 (11)	45 (11)	21 (8)	24 (9)	20 (8)	15 (6)
Serious Adverse Events								
n (%)	6 (2)	3 (1)	13 (3)	20 (5)	3 (1)	8 (3)	5 (2)	3 (1)

	Study 3107		Study 6974		Study 3109		Study 2352	
	FF/V 100/25 N = 266	FP/S 500/50 N = 262	FF/V 100/25 N = 260	FP/S 250/50 N = 259	FF/V 100/25 N = 259	FP/S 250/50 N = 252	FF/V 100/25 N = 259	FP/S 250/50 N = 252
WDAEs								
n (%)	6 (2)	3 (1)	14 (3)	16 (4)	4 (2)	8 (3)	5 (2)	1 (< 1)
Pneumonia								
n (%)	1 (< 1)	2 (< 1)	2 (< 1)	4 (< 1)	1 (< 1)	0	2 (< 1)	0

CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second; FF/V = fluticasone furoate + vilanterol; FP/S = fluticasone propionate + salmeterol; LS = least squares; MD = mean difference; mMRC = Modified Medical Research Council Dyspnea Scale; NR = not reported; SD = standard deviation; SE = standard error; SGRQ = St. George's Respiratory Questionnaire; V = vilanterol; WDAE = withdrawal due to adverse event.
Source: Clinical Study Reports for study 3107, [10] study 6974, [11] study 3109, [12] and study 2352.[13]

TABLE 2: SUMMARY OF RESULTS: STUDIES VERSUS TIOTROPIUM

	Study 5805	
	FF/V 100/25 N = 310	TIO 18 N = 313
FEV_1, 0 to 24-Hour Weighted Mean		
LS mean change from baseline (SE) day 84, L	0.117 (0.013)	0.095 (0.0138)
LS MD (95% CI)	0.022 (–0.012 to 0.055)	
P value	*P* = 0.201	
Trough FEV_1		
Weighted mean (SD) day 85, L	0.098 (0.013)	0.093 (0.014)
LS MD (95% CI)	0.005 (–0.029 to 0.039)	
P value	NR	
SGRQ Total Score		
Week 12, mean (SD) change	[redacted]	[redacted]
LS MD (95% CI)	[redacted]	
P value	[redacted]	
Symptoms (Cough)		
Mean (SD) change from baseline, weeks 1 to 12	[redacted]	[redacted]
Between-group difference of change from baseline (95% CI)	[redacted]	
P value	[redacted]	
Symptoms (Breathless)		
Mean (SD) change from baseline, weeks 1 to 12	[redacted]	[redacted]
Between-group difference of change from baseline (95% CI)	[redacted]	
P value	[redacted]	
Symptoms (Sputum)		
Mean (SD) change from baseline, weeks 1 to 12	[redacted]	[redacted]
Between-group difference of change from baseline (95% CI)	[redacted]	
P value	[redacted]	
Deaths (All-Cause)		
On treatment, n (%)	0	2
Deaths, COPD		
On treatment, n (%)	0	0
Exacerbations		
Total	[redacted]	[redacted]
Withdrawals		
Total, n (%)	19 (6)	39 (12)
Serious AEs		
n (%)	10 (3)	10 (3)
WDAEs		
n (%)	6 (2)	12 (4)
AE (Pneumonia)		
n (%)	2 (< 1)	0

AE = adverse event; CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second; FF/V = fluticasone furoate + vilanterol; LS = least squares; MD = mean difference; NR = not reported; SE = standard error; SD = standard deviation; SGRQ = St. George's Respiratory Questionnaire; TIO = tiotropium; V = vilanterol; WDAE = withdrawal due to adverse event.
Source: Clinical Study Report for study 5805.[14]

TABLE 3: SUMMARY OF RESULTS: PLACEBO-CONTROLLED

	Study 2206				Study 2207			
FEV_1, 0 to 4 Hours Weighted Mean	FF/V 100/25 N = 206	Placebo N = 207	FF 100 N = 206	V25 N = 205	FF/V 100/25 N = 204	Placebo N = 1555	FF 100 N = 204	V25 N = 203
Mean (SD) change from baseline, day 168	[redacted]							
Between-group difference (vs. placebo) (95% CI)	[redacted]				[redacted]			
P value (vs. placebo)	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Trough FEV_1								
Mean (SD) change from baseline, day 169	[redacted]							
Between-group difference (vs. placebo) (95% CI)	[redacted]				[redacted]			
P value (vs. placebo)	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
CRQ-SAS (Dyspnea)								
Mean (SD) change from baseline, day 168	[redacted]							
Between-group difference (vs. placebo) (95% CI)	[redacted]							
P value (vs. placebo)	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
CRQ-SAS (Total)								
Mean (SD) change from baseline, day 168	[redacted]							
Between-group difference (vs. placebo) (95% CI)	[redacted]							
P value (vs. placebo)	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Symptoms (Cough)								
Mean (SD) change from baseline, day 168	[redacted]							
Between-group difference (vs. placebo) (95% CI)	[redacted]							
P value (vs. placebo)	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Symptoms (Sputum)								
Mean (SD) change from baseline, day 168	[redacted]							

	Study 2206				Study 2207			
FEV_1, 0 to 4 Hours Weighted Mean	FF/V 100/25 N = 206	Placebo N = 207	FF 100 N = 206	V25 N = 205	FF/V 100/25 N = 204	Placebo N = 1555	FF 100 N = 204	V25 N = 203
	[redacted]							
Between-group difference (vs. placebo) (95% CI)	[redacted]							
P value (vs. placebo)	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Symptoms (Breathless)								
Mean (SD) change from baseline, day 168	[redacted]							
Between-group difference (vs. placebo) (95% CI)	[redacted]							
P value (vs. placebo)	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Deaths								
On treatment, n (%)	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
During follow-up, n (%)	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbations								
Patients, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawals								
Total, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAEs								
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WDAEs								
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE (Pneumonia)								
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CRQ-SAS = Chronic Respiratory Questionnaire Self-Administered Standardized; FEV_1 = forced expiratory volume in one second; FF = fluticasone furoate; FF/V = fluticasone furoate + vilanterol; LS = least squares; MD = mean difference; mMRC = Modified Medical Research Council Dyspnea Scale; SAE = serious adverse event; V = vilanterol; vs. = versus; WDAE = withdrawal due to adverse event.
Source: Clinical Study Reports for studies 2206[15] and 2207.[16]

TABLE 4: SUMMARY OF RESULTS: VILANTEROL-CONTROLLED

	Study 2871		Study 2970	
	FF/V 100/25 N = 403	V25 N = 409	FF/V 100/25 N = 403	V25 N = 409
Trough FEV_1				
Mean (SD) change from baseline, week 52	0.018 (0.0112)	–0.040 (0.0114)	0.005 (0.0115)	–0.019 (0.0116)
Between-group difference of change from baseline (95% CI)	0.058 (0.027 to 0.090)		0.024 (–0.008 to 0.056)	
P value	*P* < 0.001		*P* = 0.143	
Dyspnea Scores (IVRS Diary)				
LS mean (SE), weeks 1 to 52	–0.31 (0.02) N = 399	–0.23 (0.02) N = 407	–0.20 (0.02) N = 401	–0.09 (0.02) N = 407
P value	*P* = 0.019		*P* < 0.001	
Symptoms (% 24-Hour Periods With Increased Sputum)				
Mean (SD) baseline	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) weeks 1 to 52	[redacted]	[redacted]	[redacted]	[redacted]
P value				
Deaths (All-Cause)				
On treatment, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
During follow-up, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Deaths, COPD				
On treatment, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Moderate/Severe Exacerbations				
Annual rate, LS mean	0.70 N = 401	1.05 N = 407	0.90 N = 401	1.14 N = 402
	P < 0.001		*P* = 0.024	
All Exacerbations				
Annual rate, LS mean	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	
Time to First Moderate or Severe Exacerbation				
Hazard ratio (95% CI)	0.72 (0.59 to 0.89)		0.80 (0.66 to 0.99)	
	P = 0.002		*P* = 0.036	
Moderate Exacerbations				
Total	[redacted]	[redacted]	[redacted]	[redacted]
Number of in-patient hospital days (ICU)	[redacted]	[redacted]	[redacted]	[redacted]
Number of in-patient hospital days (ward)	[redacted]	[redacted]	[redacted]	[redacted]
Severe Exacerbations				
Total	[redacted]	[redacted]	[redacted]	[redacted]
Number of in-patient hospital days (ICU)	[redacted]	[redacted]	[redacted]	[redacted]
Number of in-patient hospital days (ward)	[redacted]	[redacted]	[redacted]	[redacted]

	Study 2871		Study 2970	
	FF/V 100/25 N = 403	V25 N = 409	FF/V 100/25 N = 403	V25 N = 409
Withdrawals				
Total, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Serious AEs				
n (%)	56 (14)	60 (15)	67 (17)	66 (16)
WDAEs				
n (%)	29 (7)	22 (5)	35 (9)	25 (6)
AE (Pneumonia)				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second; FF = fluticasone furoate; FF/V = fluticasone furoate + vilanterol; ICU = intensive care unit; IVRS = interactive voice response system; LS = least squares; mMRC = Modified Medical Research Council Dyspnea Scale; SD = standard deviation; SE = standard error; V = vilanterol; WDAE = withdrawal due to adverse event.
Source: Clinical Study Reports for study 2871[17] and study 2970.[18]

TABLE 5: SUMMARY OF RESULTS: PLACEBO-CONTROLLED (CROSSOVER DESIGN)

	Study 946	
FEV_1, 0 to 24-Hour Weighted Mean	FF/V 100/25 N = 33	Placebo N = 51
LS mean (SE) baseline	1.517 (0.0282)	1.297 (0.0240)
LS mean (SE) change from baseline, day 29	0.164 (0.0282)	–0.056 (0.0240)
Between-group difference of change from baseline (95% CI)	0.220 (0.165 to 0.275)	
P value	*P* < 0.001	
Trough FEV_1		
LS mean (SE) day 29	1.506 (0.035)	1.328 (0.029)
LS mean (SE) change from baseline, day 29	0.153 (0.035)	–0.024 (0.029)
Between-group difference of change from baseline (95% CI)	0.177 (0.097 to 0.257)	
P value	*P* < 0.001	
Symptoms		
	NR	NR
Deaths (All-Cause)		
On treatment, n (%)	0	0
Deaths, COPD		
On treatment, n (%)	0	0
Moderate Exacerbations		
Total	NR	NR
Severe Exacerbations		
Total	NR	NR
Withdrawals		
Total, n (%)	2 (6)	3 (6)
SAEs		
n (%)	0	0

	Study 946	
FEV_1, 0 to 24-Hour Weighted Mean	**FF/V 100/25 N = 33**	**Placebo N = 51**
WDAEs		
n (%)	0	0
Pneumonia		
n (%)	0	0

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second; FF/V = fluticasone furoate + vilanterol; LS = least squares; SE = standard error; WDAE = withdrawal due to adverse event.
Source: Clinical Study Report for study 946.[19]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Chronic obstructive pulmonary disease (COPD) is a respiratory disorder characterized by progressive, partially reversible airway obstruction and lung hyperinflation, systemic manifestations, and increasing frequency and severity of exacerbations.[1, 2] Pathological changes in the lung vary between individuals, but usually involve a combination of airway inflammation (chronic bronchitis) and parenchymal destruction (emphysema).[20] There is significant overlap of COPD subtypes, with many individuals presenting with features of both chronic bronchitis and emphysema, as well as asthma, which differs fundamentally from COPD.[2] COPD is largely caused by smoking and is associated with multiple comorbid conditions (e.g., diabetes, ischemic heart disease, muscle wasting, bone loss, anemia, cancer, anxiety, and depression).[2, 21]

COPD is a major public health problem and is a leading cause of morbidity and mortality worldwide, comprising an economic and social burden that is both substantial and increasing.[22] According to a 2009 Statistics Canada report, COPD affects 4% of the Canadian populationaged 35 years and older.[3] Among COPD patients in Canada aged 35 to 79 years, 7% had stage II (moderate) or higher COPD.[23] Diagnosing and determining the severity of COPD typically requires the use of spirometry. The two indicators necessary for establishing a diagnosis of COPD are forced expiratory volume in one second (FEV_1), which is the amount of air that one can expel in one second, and forced vital capacity (FVC), which is the amount of air that one can expel upon full inspiration with no limit to duration of expiration. A post-bronchodilator FEV_1/FVC ratio of less than 0.7 indicates airway obstruction. The Canadian Thoracic Society classification of COPD severity is summarized in Table 6.

TABLE 6: CANADIAN THORACIC SOCIETY CLASSIFICATION OF COPD SEVERITY BY SYMPTOMS, DISABILITIES, AND IMPAIRMENT OF LUNG FUNCTION

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

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second of expiration; FVC = forced vital capacity; N/A = not available.
Source: O'Donnell et al., 2007.[1]

COPD is associated with an increased risk of mortality and was ranked as the fourth leading cause of death in Canada in 2004.[1] By 2020, COPD is projected to become the third leading cause of death worldwide.[22] COPD is associated with high rates of admissions and readmissions to hospital (i.e., of all COPD patients hospitalized in 2006-2007, 18% of COPD patients were readmitted once and 14% were

admitted twice).[24] Hospital admissions for COPD exacerbations averaged a 10-day length of stay at a cost of $10,000 per stay. The total cost of COPD hospitalizations in Canada is estimated at $1.5 billion a year.[25]

1.2 Standards of Therapy

The goals of COPD management are to prevent disease progression, reduce frequency and severity of exacerbations, alleviate symptoms, improve exercise tolerance and daily activity, treat exacerbations and complications, improve health status, and reduce mortality.[1] 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.[2] Regular exercise with cardiorespiratory conditioning can improve functional status and sensation of dyspnea in COPD patients more than use of medications alone.

Bronchodilators form the mainstay of pharmacotherapy for COPD [2] and include short-acting beta-agonists (SABAs) such as salbutamol and antimuscarinic drugs (SAMAs) such as ipratropium. Long-acting beta-agonists (LABAs) such as salmeterol, formoterol, and indacaterol, or antimuscarinic (LAAC) drugs such as tiotropium and glycopyrronium, as well as combinations of fixed-dose LABAs and inhaled corticosteroids (LABA plus ICS) such as fluticasone/salmeterol (Advair) or budesonide/formoterol (Symbicort), are the most commonly used treatments for COPD in Canada. Antimuscarinic and beta-agonist drugs are often used in combination for maximal improvement in dyspnea and function. Inhaled steroids may not be useful for mild disease; however, they may have more of a role in the management of moderate to severe COPD, or in those with persistent symptoms.[4-6] There may also be a subpopulation of COPD patients who have concomitant asthma or airway eosinophilia, where ICS use may be beneficial.[7-9] Phosphodiesterase inhibitors (theophylline and, more recently, roflumilast) are adjunctive therapies for COPD management that may be more effective in those with demonstrable neutrophilic airway inflammation. Inhaled medications are most commonly delivered as pressurized metered-dose inhalers and dry powder inhalers.

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

Acute exacerbations of COPD are managed with optimized bronchodilator therapy, oral or parenteral corticosteroids, and antibiotics.[2]

1.3 Drug

Breo Ellipta is a combination of an inhaled corticosteroid (ICS), fluticasone furoate, and a long-acting beta2-agonist (LABA), vilanterol. The ICS component is used for its potent anti-inflammatory properties, and the LABA acts as a long-acting bronchodilator. Fluticasone furoate is a long-acting ICS, and thus in combination with the LABA, this inhaler can be administered once daily. The other two marketed ICS/LABA combinations approved for COPD in Canada, Advair and Symbicort, are administered twice daily (see Table 7 for further comparison of ICS/LABA combinations).

Indication under review
Breo Ellipta (fluticasone furoate/vilanterol) is indicated for the long-term once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, and to reduce exacerbations of COPD in patients with a history of exacerbations.
Listing criteria requested by sponsor
For the maintenance treatment of moderate to severe COPD, to reduce exacerbations.

TABLE 7: KEY CHARACTERISTICS OF BREO ELLIPTA, ADVAIR, AND SYMBICORT

	Fluticasone Furoate/Vilanterol (Breo Ellipta)	Fluticasone Propionate/Salmeterol (Advair)	Budesonide/Formoterol (Symbicort)
Mechanism of Action	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 in the lungs leads to bronchodilation	ICS: anti-inflammatory effects may treat the inflammation associated with COPD LABA: stimulation of beta2 in the lungs leads to bronchodilation
Indication[a]	COPD	COPD	COPD
Route of Administration	Inhaled	Inhaled	Inhaled
Recommended Dose	100/25 mcg once daily	250/50 mcg or 500/50 mcg twice daily	160/4.5 mcg twice daily
Serious Side Effects/ Safety Issues	ICS component: • Increased risk of pneumonia • Immunosuppression • Adrenal suppression LABA component: • Increased risk of asthma-related death	ICS component: • Increased risk of pneumonia • Immunosuppression • Adrenal suppression LABA component: • Increased risk of asthma-related death	ICS component: • Increased risk of pneumonia • Immunosuppression • Adrenal suppression LABA component: • Increased risk of asthma-related death
Other	Delivery device: Ellipta	Delivery device: Accuhaler/DISKUS	Delivery device: Turbuhaler

COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; LABA = long-acting beta-agonist.
[a] Health Canada indication.
Source: Product monographs for Breo Ellipta, Advair, and Symbicort.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of fluticasone furoate/vilanterol (Breo Ellipta) for the treatment of patients with COPD, including chronic bronchitis and/or emphysema.

2.2 Methods

Studies selected for inclusion in the systematic review included the pivotal studies in support of the Health Canada indication provided in the manufacturer's submission to the CADTH Common Drug Review (CDR) as well as those meeting the selection criteria presented in Table 8.

TABLE 8: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Patients diagnosed with COPD, including chronic bronchitis and/or emphysema **Subgroups** Age, sex, BMI, COPD severity, chronic bronchitis, emphysema, smoking status, bronchodilator reversibility, concomitant COPD medication use, indicators of asthma
Intervention	Fluticasone furoate 100 mcg/vilanterol 25 mcg once daily, alone or in combination with conventional therapies
Comparators	The following comparators used alone or in combination (as appropriate): LABA (e.g., salmeterol, formoterol, indacaterol) SABA (e.g., salbutamol) LAAC (e.g., tiotropium, glycopyrronium, aclidinium) SAAC (e.g., ipratropium) ICS (e.g., fluticasone propionate, fluticasone furoate, budesonide) Roflumilast Theophylline Placebo
Outcomes	**Key efficacy outcomes** Mortality (all-cause) Mortality due to COPD Health care resource utilization (e.g., hospitalization, emergency room visits) Exacerbations, and time to first exacerbation Quality of life Spirometry (e.g., FEV_1, inspiratory capacity) Symptoms (including dyspnea) Exercise tolerance **Other efficacy outcomes** Use of rescue medication, patient adherence/satisfaction, days of missed work/school **Harms outcomes** SAEs WDAEs AEs
Study Design	Published and unpublished DB RCTs

AE = adverse event; BMI = body mass index; COPD = chronic obstructive pulmonary disease; DB = double-blind; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; LAAC = long-acting anticholinergics; LABA = long-acting beta-agonists; RCT = randomized controlled trial; SAAC = short-acting anticholinergics; SABA = short-acting beta-agonists; SAE = serious adverse event; SC = subcutaneously; WDAE = withdrawal due to adverse event.

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

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

Methodological filters were not applied. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on March 20, 2014. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on July 16, 2014. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters):

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Databases (free)
- Internet Search

Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 9 through Table 14; excluded studies (with reasons) are presented in APPENDIX 4: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings From the Literature

A total of 10 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 9 through Table 14 and described in section 3.2. A list of excluded studies is presented in APPENDIX 4: EXCLUDED STUDIES.

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

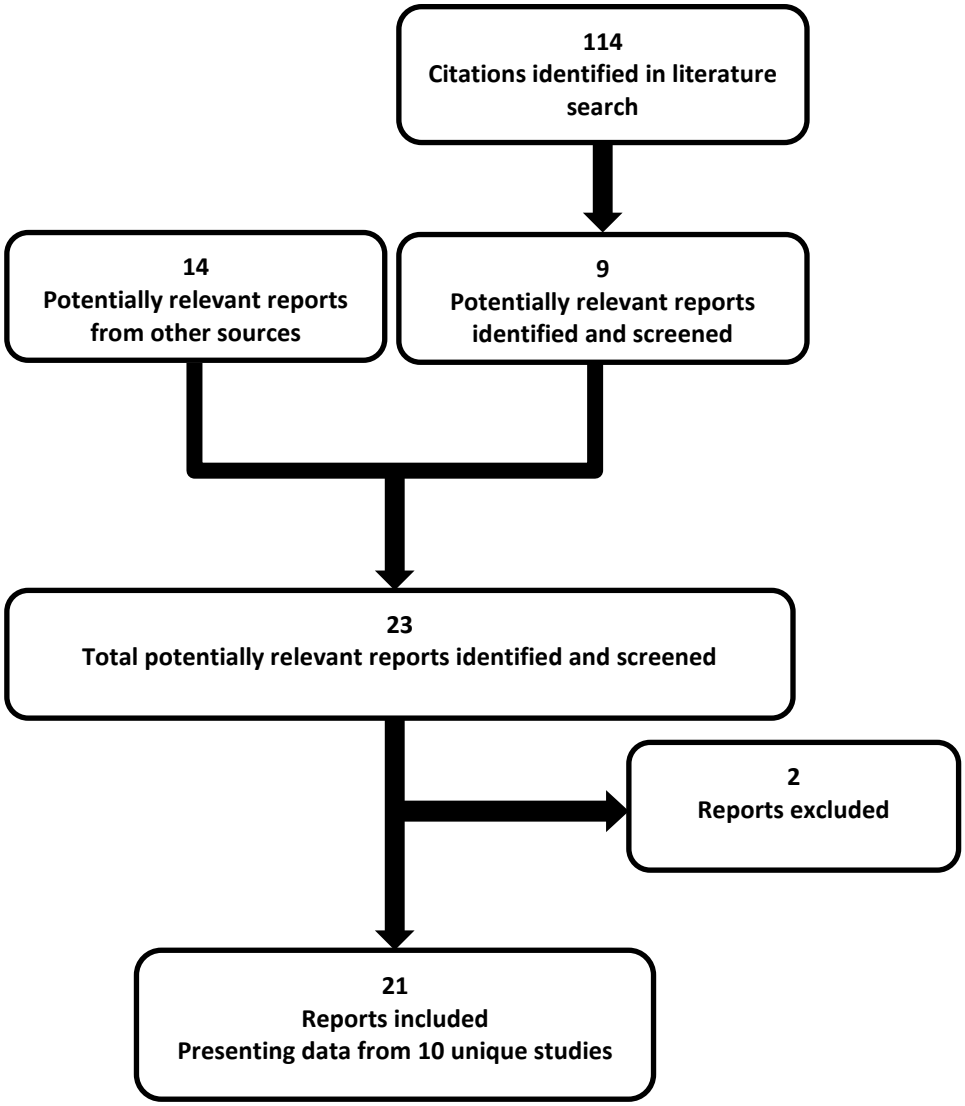

TABLE 9: DETAILS OF INCLUDED STUDIES: ACTIVE CONTROL (FLUTICASONE PROPIONATE PLUS SALMETEROL AS CONTROL)

	Study 3107	Study 6974
Study Design	DB RCT	DB RCT
Locations	61 centres (Europe and Asia)	68 centres (EU, USA)
Study Period	Feb. 2011 to Oct. 2011	Oct. 15, 2012 to Jun. 17, 2013
Randomized (N)	528	828
Inclusion Criteria	• ≥ 40 years of age at screening • Clinical history of COPD • Current or prior history of ≥ 10 pack-years of cigarette smoking • Post-salbutamol FEV_1/FVC of ≤ 0.70 • Post-salbutamol FEV_1 ≤ 70% of predicted • At least one moderate COPD exacerbation (requiring treatment with oral corticosteroid/antibiotic) or severe exacerbation (leading to hospitalization) within the past three years	≥ 40 years of age at screening • Clinical history of COPD • Current or prior history of ≥ 10 pack-years of cigarette smoking • Post-salbutamol FEV_1/FVC of ≤ 0.70 • Post-salbutamol FEV_1 ≤ 70% of predicted
Exclusion Criteria	• Hospitalization due to COPD within 12 weeks of screening, or acute worsening of COPD (defined as use of corticosteroids or antibiotics) within 6 weeks of screening • Historical or current evidence of uncontrolled or clinically significant disease that, in the opinion of the investigator, would put the safety of the patient at risk through participation, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the study; this included cardiovascular disease (i.e., patients requiring implantable cardioverter defibrillator or pacemaker requiring a rate set > 60 bpm), or hypertension	
Intervention	FF/V 100/25 mcg once daily	
Comparator(s)	FP/S 500/50 mcg twice daily (Accuhaler/DISKUS)	FP/S 250/50 mcg twice daily (Accuhaler/DISKUS)
Phase		
Run-in	2 weeks (placebo)	
Double-blind	12 weeks	
Follow-up	1 week	
Primary End Point	Change from baseline trough in 24-hour weighted-mean FEV_1 on treatment day 84	
Other End Points	1) Time to 100 mL increase in FEV_1 from baseline from 0 to 4 hours on day 1; and 2) Change from baseline in trough FEV_1 on day 85; i.e., the comparison of the FEV_1 recorded 24 hours post-dose on day 84 with the baseline measure. Other: • St. George's Respiratory Questionnaire for COPD • Rescue-free 24-hour periods.	1) Time to 100 mL increase in FEV_1 from baseline from 0 to 4 hours on day 1; and 2) Change from baseline in trough FEV_1 on day 85; i.e., the comparison of the FEV_1 recorded 24 hours post-dose on day 84 with the baseline measure.
Publications	August 2014[26]	None

bpm = beats per minute; COPD = chronic obstructive pulmonary disease; DB = double-blind; FEV_1 = forced expiratory volume in one second; FF = fluticasone furoate; FF/V = fluticasone furoate + vilanterol; FP/S = fluticasone propionate plus salmeterol; FVC = forced vital capacity; RCT = randomized controlled trial; V = vilanterol.
Source: Clinical Study Reports for study 3107, [10] study 6974.[11]

TABLE 10: DETAILS OF INCLUDED STUDIES: ACTIVE CONTROL (FLUTICASONE PROPIONATE PLUS SALMETEROL AS CONTROL)

	Study 3109	Study 2352
Study Design	DB RCT	DB RCT
Locations	52 centres (Europe and US)	49 centres: EU, US, South Africa
Study Period	Mar. 2011 to Dec. 2011	Mar. 2011 to Jan. 2012
Randomized (N)	519	511
Inclusion Criteria	≥ 40 years of age at screening • Clinical history of COPD • Current or prior history of ≥ 10 pack-years of cigarette smoking • Post-salbutamol FEV_1/FVC of ≤ 0.70 • Post-salbutamol FEV_1 ≤ 70% of predicted	
Exclusion Criteria	• Hospitalization due to COPD within 12 weeks of screening, or acute worsening of COPD (defined as use of corticosteroids or antibiotics) within 6 weeks of screening • Historical or current evidence of uncontrolled or clinically significant disease that, in the opinion of the investigator, would put the safety of the patient at risk through participation, or which would affect the efficacy or safety analysis if the disease or condition exacerbated during the study. This included cardiovascular disease (i.e., patients requiring implantable cardioverter defibrillator or pacemaker requiring a rate set > 60 bpm), or hypertension	
Intervention	FF/V 100/25 mcg once daily	
Comparator(s)	FP/S 250/50 mcg twice daily (Accuhaler/DISKUS)	
Phase		
Run-in	2 weeks (placebo)	
Double-blind	12 weeks	
Follow-up	1 week	
Primary End Point	Change from baseline trough in 24-hour weighted-mean FEV_1 on treatment day 84	
Other End Points	Time to 100 mL increase in FEV_1 from baseline Other: [redacted]	
Publications	None	

bpm = beats per minute; COPD = chronic obstructive pulmonary disease; DB = double-blind; EU = European Union; FEV_1 = forced expiratory volume in 1 second; FF = fluticasone furoate; FF/V = fluticasone furoate + vilanterol; FP/S = fluticasone propionate plus salmeterol; FVC = forced vital capacity; RCT = randomized controlled trial; V = vilanterol.
Source: Clinical Study Reports for study 3109 [12] and 2352.[13]

TABLE 11: DETAILS OF INCLUDED STUDIES: ACTIVE CONTROL (TIOTROPIUM AS CONTROL)

	Study 5805
Study Design	DB RCT
Locations	56 centres: US, Canada, Europe
Study Period	April 2 2012 to Dec. 21 2012
Randomized (N)	623
Inclusion Criteria	• ≥ 40 years of age at screening • Clinical history of COPD • Current or prior history of ≥ 10 pack-years of cigarette smoking • Post-salbutamol FEV_1/FVC of ≤ 0.70 • Post-salbutamol FEV_1 30% to 70% of predicted • Diagnosed cardiovascular disease or prior cardiovascular event
Exclusion Criteria	Hospitalization due to COPD within 12 weeks of screening, or acute worsening of COPD (defined as use of corticosteroids or antibiotics) within 6 weeks of screening
Intervention	FF/V 100/25 mcg once daily
Comparator(s)	Tiotropium 18 once daily (HandiHaler)
Phase	
Run-in	2 weeks
Double-blind	12 weeks
Follow-up	1 week
Primary End Point	Change from baseline trough in 24-hour weighted-mean FEV_1 on treatment day 84
Other End Points	1) Time to 100 mL increase in FEV_1 from baseline from 0 to 4 hours on day 1; and 2) Change from baseline in trough FEV_1 on day 85, i.e., the comparison of the FEV_1 recorded 24 hours post-dose on day 84 with the baseline measure.
Publications	None

bpm = beats per minute; COPD = chronic obstructive pulmonary disease; DB = double-blind; FEV_1 = forced expiratory volume in one second; FF = fluticasone furoate; FF/V = fluticasone furoate + vilanterol; FVC = forced vital capacity; RCT = randomized controlled trial; V = vilanterol.
Source: Clinical Study Reportfor study 5805.[14]

TABLE 12: DETAILS OF INCLUDED STUDIES: PLACEBO-CONTROLLED

		Study 2206	Study 2207
DESIGNS & POPULATIONS	**Study Design**	DB RCT	DB RCT
	Locations	221 centres: US, Europe, South America, Asia	138 centres: US, Europe, Asia
	Study Period	Oct. 19, 2009 to Feb. 16, 2011	Oct. 19, 2009 to Mar. 16, 2011
	Randomized (N)	1030	1224
	Inclusion Criteria	• ≥ 40 years of age at screening • Clinical history of COPD • Current or prior history of ≥ 10 pack-years of cigarette smoking • Post-salbutamol FEV_1/FVC of ≤ 0.70 • Post-salbutamol FEV_1 ≤ 70% of predicted • Score of ≥ 2 on mMRC Dyspnea Scale	

		Study 2206	Study 2207
	Exclusion Criteria	• Hospitalized due to poorly controlled COPD within 12 weeks of visit 1 • Acute worsening of COPD managed with corticosteroids or antibiotics or requiring treatment prescribed by a physician • COPD exacerbation/lower respiratory tract infection during the run-in period [redacted]	
DRUGS	**Intervention**	FF/V 50/25 mcg once daily FF/V 100/25 mcg once daily	FF/V 100/25 mcg once daily FF/V 200/25 mcg once daily
	Comparator(s)	FF 100 mcg once daily or V 25 mcg once daily or placebo once daily	FF 100 mcg once daily or FF 200 mcg once daily or V 25 mcg once daily or placebo once daily
	Phase		
	Run-in	2 weeks	
	Double-blind	12 weeks	
	Follow-up	1 week	
OUTCOMES	**Primary End Point**	Weighted mean FEV_1 0 to 4 hours post-dose on treatment day 168 Change from baseline in trough (pre-bronchodilator and pre-dose) FEV_1, on treatment day 169	
	Other End Points	• CRQ-SAS dyspnea domain • Peak FEV_1 on treatment day 1 • Time to increase of 100 mL above baseline in FEV_1 on treatment day 1 Other: • Time to 12% change from baseline in FEV_1 on day 1 • Weighted mean clinic visit FEV_1 0 to 4 hours post-dose on treatment days 1, 14, 56, 84 • Change from baseline in clinic-visit trough FEV_1 on treatment days 2, 7, 14, 28, 56, 84, 112, and 140 • Percentage of symptom-free 24-hour periods during each week of treatment and over entire 24-week treatment period • Percentage of rescue-free 24-hour periods during each week of treatment and over entire 24-week treatment period • Symptom scores (breathlessness, cough, sputum) averaged over each week and over 24-week treatment period • Number of occasions rescue salbutamol during a 24-hour period averaged over each week and over 24-week treatment period • Percentage of nights with no night awakenings requiring salbutamol during each week of treatment and over 24-week treatment period • Number of nighttime awakenings requiring salbutamol averaged over each week of treatment and over 24-week treatment period • CRQ-SAS other domains and total score.	
NOTES	**Publications**	Kerwin 2013[27, 28]	Martinez 2013[29, 30]

COPD = chronic obstructive pulmonary disease; CRQ-SAS = Chronic Respiratory Questionnaire Self-Administered Standardized; FF = fluticasone furoate; FF/V = fluticasone furoate + vilanterol; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; mMRC = Modified Medical Research Council; V = vilanterol.
Source: Clinical Study Reports for studies 2206[15] and 2207.[16]

TABLE 13: DETAILS OF INCLUDED STUDIES: VILANTEROL-CONTROLLED

	Study 2871	Study 2970
Study Design	DB RCT	DB RCT
Locations	167 centres: North America (Canada), South America, Europe, Asia, Africa	183 centres: North America (Canada), South America, Europe, Australia, South Africa
Study Period	Sept. 25, 2009 to Oct. 31, 2011	Sept. 25, 2009 to Oct. 17, 2011
Randomized (N)	1,622	1,633
Inclusion Criteria	• ≥ 40 years of age at screening • Clinical history of COPD • Current or prior history of ≥ 10 pack-years of smoking • Post-salbutamol FEV_1/FVC of ≤ 0.70 • Post-salbutamol FEV_1 ≤ 70% of predicted • ≥ 1 COPD exacerbation in 12 months prior to visit 1 requiring either systemic/oral corticosteroids, antibiotics, and/or hospitalization	
Exclusion Criteria	• Moderate or severe COPD exacerbation that had not resolved at least 14 days prior to screening visit 1 or for which the last dose of oral corticosteroids was not taken at least 30 days prior to screening visit 1; pneumonia and/or moderate or severe COPD exacerbation at screening visit 1 • Uncontrolled hypertension; uncontrolled other diseases/abnormalities	
Intervention	FF/V 50/25 mcg once daily FF/V 100/25 mcg once daily FF/V 200/25 mcg once daily	
Comparator(s)	V 25 mcg once daily	
Phase		
Run-in	4 weeks (FP/S 250/50 twice daily)	
Double-blind	52 weeks	
Follow-up	1 week	
Primary End Point	Annual rate of moderate/severe exacerbations	
Other End Points	• Time to first moderate or severe exacerbation • Annual rate of exacerbations requiring systemic/oral CS • Change from baseline in trough FEV_1 at visit 11 Other: • Annual rate of severe exacerbations • Annual rate of all exacerbations (mild, moderate, severe) • Time-to-onset of multiple moderate/severe exacerbations • Change from baseline in trough FEV_1 at visits 3 to 10 • Number of nighttime awakenings due to symptoms of COPD averaged over each 4-week treatment interval and over the entire 52-week treatment period • Percentage of nights with no nighttime awakenings due to symptoms of COPD averaged over each 4-week treatment interval and over 52-week treatment period • Number of occasions of rescue salbutamol used during a 24-hour period averaged over each 4-week treatment interval and over the entire 52-week treatment period • Percentage of rescue-free 24-hour periods during each 4-week treatment interval and over the entire 52-week treatment period • Mean dyspnea score averaged over each 4-week treatment interval and over the entire 52-week treatment period	

	Study 2871	Study 2970
	• Percentage of 24-hour periods with increased sputum during each 4-week treatment interval and over the entire 52-week treatment period • Percentage of 24-hour periods with increase in yellow/green sputum colour during each 4-week treatment interval and over the entire 52-week treatment period	
Publications	Dransfield 2013[31]	Dransfield 2013[31]

COPD = chronic obstructive pulmonary disease; DB = double-blind; FEV_1 = forced expiratory volume in one second; FF = fluticasone furoate; FF/V = fluticasone furoate + vilanterol; FVC = forced vital capacity; mMRC = Modified Medical Research Council; RCT = randomized controlled trial; V = vilanterol.
Source: Clinical Study Reports for study 2871[17] and study 2970.[18]

TABLE 14: DETAILS OF INCLUDED STUDIES: CROSSOVER

	Study 946
Study Design	DB RCT (crossover)
Locations	8 centres: USA
Study Period	Jan. 25, 2010 to Jul. 1, 2010
Randomized (N)	84
Inclusion Criteria	• ≥ 40 years of age at screening • Clinical history of COPD • Current or prior history of ≥ 10 pack-years of cigarette smoking a dyspnea score of ≥ 2 on the Modified Medical Research Council Dyspnea Scale (mMRC, 0 to 4 scale)
Exclusion Criteria	Hospitalized due to poorly controlled COPD within 12 weeks of screening; poorly controlled COPD
Intervention	FF/V 50/25 mcg once daily, or FF/V 100/25 mcg once daily, or FF/V 200/25 mcg once daily
Comparator(s)	Placebo
Phase	
Run-in	2 weeks (placebo)
DB	4 weeks plus 4 weeks plus 4 weeks (2-week washout between each)
Follow-up	1 week
Primary End Point	Weighted-mean AUC for 0–24 h serial FEV_1 at the end of 28-day treatment period
Other End Points	• Change from period baseline in clinic-visit trough FEV_1 at end of each 28-day treatment period • 24-hour serial FEV_1 at end of each 28 days Other: • 0 to 4 h peak FEV_1 at end of each 28-day treatment period • Non-linear mixed effects population dose-response analysis of time-adjusted AUC (i.e., weighted mean) for 24-hour serial FEV_1 over period days 28 to 29 and change from period baseline in clinic-visit trough FEV_1 on period day 29 • Non-linear mixed effects population dose-time-FEV_1 response analysis at the end of each 28-day treatment period (period days 28 to 29).
Publications	Boscia 2012[32]

AUC = area under the curve; COPD = chronic obstructive pulmonary disease; DB = double-blind; FEV_1 = forced expiratory volume in one second; FF = fluticasone furoate; FF/V = fluticasone furoate + vilanterol; FVC = forced vital capacity; mMRC = Modified Medical Research Council; RCT = randomized controlled trial; V = vilanterol.
Note: Five additional reports were included: Health Canada Review,[33] Food and Drug Administration (FDA) statistical and clinical reviews, [34, 35] manufacturer's submission.[36]
Source: Clinical Study Reportfor study 946.[19]

3.2 Included Studies

3.2.1 Description of Studies

Ten DB RCTs met the inclusion criteria for this systematic review. All studies were multi-centre, and manufacturer-sponsored. Five were active-controlled, three were placebo-controlled, and two had vilanterol as control, with further details on all subsequently provided.

a) Active-Controlled

Of the five active-controlled studies, four had fluticasone propionate plus salmeterol as a control (study 6974, 3107, 2852, and 3109) and one had tiotropium as a control (study 5805). The active-controlled studies were all 12 weeks in duration. Only one of the fluticasone propionate plus salmeterol studies was described as a non-inferiority analysis (study 3107), while the others appeared to employ a non-inferiority design but did not specify. The comparison to tiotropium (study 5805) was described as powered for superiority by the manufacturer. In the fluticasone propionate plus salmeterol-controlled studies, randomization was stratified by baseline reversibility to bronchodilator, while in study 5805, randomization was stratified by baseline reversibility and by three-year exacerbation history (Table 9, Table 10, Table 11).

b) Placebo-Controlled

Three studies had a placebo control (study 2206, 2207, and 946). Studies 2206 and 2207 were of identical design, and aside from a fluticasone furoate plus vilanterol and a placebo group, also had a fluticasone furoate group and a vilanterol group, at the doses used in the fluticasone furoate plus vilanterol combination. Randomization was stratified by smoking status. These studies had a 24-week treatment duration. The investigators did not explicitly state whether superiority for fluticasone furoate plus vilanterol versus placebo was being tested (Table 12). Study 946 was a small crossover study (Table 14) with three different doses of fluticasone furoate plus vilanterol and placebo as groups. Patients were treated for four weeks with each intervention. The design of study 946 is illustrated in **Error! Reference source not found.** below.

FIGURE 2: HZC110946 STUDY DESIGN

[redacted]

Figure 2 contained confidential data and was removed at the manufacturer's request.

c) Vilanterol-Control

Two studies (studies 2871 and 2970) compared fluticasone furoate plus vilanterol to vilanterol, over a treatment period of 52 weeks. Randomization in these studies was stratified by smoking status. These were superiority studies (Table 13).

3.2.2 Populations

a) Inclusion and Exclusion Criteria

Active-Controlled Studies

In all studies, patients had to be at least 40 years old and have a confirmed diagnosis of COPD. Patients were also to have a minimum smoking history of 10 pack-years. All of these studies require a post-salbutamol FEV_1 of 70% or less and an FEV_1/FVC ratio of 0.70 or less. Study 3107 required patients to have at least one moderate COPD exacerbation (requiring treatment with oral corticosteroid or

antibiotic) or severe exacerbation (leading to hospitalization) within the past three years, while the others did not specify. All studies excluded patients who had a hospitalization for COPD within 12 weeks of screening, or a need for oral corticosteroids or antibiotics within 6 weeks of screening. Patients were also excluded during the run-in if their compliance with the placebo device fell below 80%.

Study 5805 was the only one of all 10 included studies that specifically enrolled a population that had diagnosed cardiovascular disease or a prior cardiovascular event.

Placebo-Controlled Studies
In studies 2206 and 2207, patients had to be at least 40 years old and have a confirmed diagnosis of COPD. Patients were also to have a minimum smoking history of 10 pack-years. All of these studies require a post-salbutamol FEV_1 of 70% or less and an FEV/FVC ratio of 0.70 or less. Studies did not specify that patients had to have a specific exacerbation history, but they did exclude patients who had an unresolved exacerbation. Patients were also excluded during the run-in if their compliance with the placebo device fell below 80%.

In the crossover study (study 946), patients had to be at least 40 years old and have confirmed diagnosis of COPD. Patients were also to have a minimum smoking history of 10 pack-years, and a post-salbutamol FEV_1 of 70% or less and an FEV/FVC ratio of 0.70 or less. Study 946 did not specify that patients had to have a specific exacerbation history, and the study excluded patients with poorly controlled COPD.

Vilanterol-Controlled
In studies 2871 and 2970, patients had to be at least 40 years old and have a confirmed diagnosis of COPD. Patients were also to have a minimum smoking history of 10 pack-years, and a post-salbutamol FEV_1 of 70% or less and an FEV/FVC ratio of 0.70 or less. Studies specified that patients had to have at least one exacerbation within 12 months of screening, an exacerbation requiring systemic corticosteroids, antibiotics, or hospitalization. They also excluded patients who had a moderate to severe exacerbation that had not resolved at least 14 days prior to screening, or for which the last dose of oral steroids was not at least 30 days prior to screening. [redacted].

b) Baseline Characteristics
Patients across the studies were in their early to mid-60s (range: 61.3 to 64.0 years of age), with the exception of the crossover study (study 946), where patients were 57.9 years old at baseline. The majority of patients were male in all studies, with the exception of study 946, where 46% of patients were male.

Where reported, many of the studies had similar proportions of patients with chronic bronchitis (38% to 75% across groups within studies) or emphysema (20% to 68% across groups within studies). In the studies reporting smoking history, there were consistently more current smokers (37% to 82% across groups within studies) than former smokers (18% to 63%).

Within studies, baseline characteristics were comparable between groups. In the placebo-controlled studies, there were some numerical differences with respect to COPD type, such as a low of 56% of fluticasone furoate patients with chronic bronchitis, to a high of 65% in the vilanterol group in study 2206. The detailed baseline characteristics of included studies are presented in Table 15 to Table 18.

TABLE 15: SUMMARY OF BASELINE CHARACTERISTICS: ACTIVE-CONTROLLED (FLUTICASONE PROPIONATE PLUS SALMETEROL)

	Study 3107		Study 6974		Study 3109		Study 2352	
	FF/V 100/25 N = 266	FP/S 500/50 N = 262	FF/V 100/25 N = 412	FP/S 250/50 N = 416	FF/V 100/25 N = 260	FP/S 250/50 N = 259	FF/V 100/25 N = 259	FP/S 250/50 N = 252
Mean age, years (SD)	63.0 (8.1)	62.9 (9.1)	61.0 (8.2)	61.3 (8.4)	61.1 (7.9)	61.2 (8.3)	61.6 (9.6)	61.7 (9.1)
Male gender, n (%)	212 (80)	221 (84)	301 (73)	294 (71)	164 (63)	169 (65)	181 (70)	167 (66)
COPD Type								
Chronic bronchitis	NR	NR	NR	NR	NR	NR	NR	NR
Emphysema	NR	NR	NR	NR	NR	NR	NR	NR
Smoking Status								
Current smoker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Former smoker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease Severity								
mMRC dyspnea score, mean (SD)	NR	NR	NR	NR	NR	NR	NR	NR
Post-bronchodilator Reversibility								
Reversible	73 (28)	73 (29)	116 (28)	125 (30)	54 (21)	64 (25)	75 (29)	70 (28)
Non-reversible	186 (72)	183 (71)	294 (72)	291 (70)	201 (79)	193 (75)	181 (71)	180 (72)

COPD = chronic obstructive pulmonary disease; FF/V = fluticasone furoate + vilanterol; FP/S = fluticasone propionate plus salmeterol; mMRC = Modified Medical Research Council; NR = not reported; SD = standard deviation.
Source: Clinical Study Reports for study 3107, [10] study 6974, [11] study 3109, [12] and study 2352.[13]

TABLE 16: SUMMARY OF BASELINE CHARACTERISTICS: ACTIVE-CONTROLLED (TIOTROPIUM)

	Study 5805	
	FF/V 100/25 N = 310	TIO 18 N = 313
Mean age, years (SD)	62.9 (8.1)	62.3 (8.0)
Male gender, n (%)	193 (62)	209 (67)
COPD Type		
Chronic bronchitis	[redacted]	[redacted]
Emphysema	[redacted]	[redacted]
Both	[redacted]	[redacted]
Smoking Status		
Current smoker	[redacted]	[redacted]
Former smoker	[redacted]	[redacted]
Disease Severity		
mMRC dyspnea score, mean (SD)	NR	NR

	Study 5805	
	FF/V 100/25 N = 310	TIO 18 N = 313
Post-bronchodilator Reversibility		
Reversible	[redacted]	[redacted]
Non-reversible	[redacted]	[redacted]

COPD = chronic obstructive pulmonary disease; FF/V = fluticasone furoate + vilanterol; mMRC = Modified Medical Research Council; NR = not reported; SD = standard deviation; TIO = tiotropium.
Source: Clinical Study Report for study 5805.[14]

TABLE 17: SUMMARY OF BASELINE CHARACTERISTICS: PLACEBO-CONTROLLED

	Study 2206				Study 2207			
	FF/V 100/25 N = 206	Placebo N = 207	FF 100 N = 206	V25 N = 205	FF/V 100/25 N = 204	Placebo N = 205	FF 100 N = 204	V25 N = 203
Mean age, years (SD)	62.3 (8.5)	62.1 (8.8)	62.7 (9.5)	63.4 (9.6)	61.9 (8.8)	61.9 (8.1)	61.8 (8.3)	61.2 (8.6)
Male gender, n (%)	137 (67)	141 (68)	132 (64)	140 (68)	144 (71)	152 (74)	150 (74)	151 (74)
COPD Type								
Chronic bronchitis	127 (62)	128 (62)	116 (56)	132 (65)	143 (70)	133 (65)	152 (75)	140 (69)
Emphysema	135 (66)	127 (61)	140 (68)	127 (62)	109 (53)	126 (61)	118 (58)	113 (56)
Smoking Status								
Current smoker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Former smoker	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease Severity								
mMRC dyspnea score, mean (SD)	2.4 (0.6)	2.3 (0.6)	2.4 (0.5)	2.3 (0.5)	2.4 (0.5)	2.4 (0.6)	2.4 (0.5)	2.4 (0.5)
Post-bronchodilator Reversibility								
Reversible	66 (32)	77 (38)	71 (34)	64 (31)	58 (29)	61 (30)	57 (29)	60 (30)
Non-reversible	138 (68)	128 (62)	135 (66)	140 (69)	142 (71)	142 (70)	142 (71)	140 (70)

COPD = chronic obstructive pulmonary disease; FF = fluticasone furoate; FF/V = fluticasone furoate + vilanterol; FVC = forced vital capacity; mMRC = Modified Medical Research Council; SD = standard deviation; V = vilanterol.
Source: Clinical Study Reports for studies 2206[15] and 2207.[16]

TABLE 18: SUMMARY OF BASELINE CHARACTERISTICS — VILANTEROL-CONTROLLED/CROSSOVER

Title	Study 2871		Study 2970		Study 946	
	FF/V 100/25 N = 403	V25 N = 409	FF/V 100/25 N = 403	V25 N = 409	FF/V 100/25	PLACEBO
Mean age, years (SD)	63.6 (9.1)	63.6 (9.4)	64.0 (9.3)	63.6 (9.3)	57.9 (9.2)	
Male gender, n (%)	231 (57)	239 (58)	222 (55)	235 (57)	25 (46)	
COPD Type						
Chronic bronchitis	266 (66)	262 (64)	281 (70)	287 (71)	35 (65)	
Emphysema	228 (57)	229 (56)	207 (52)	201 (50)	34 (63)	
Smoking Status						
Current smoker	174 (43)	174 (43)	185 (46)	190 (46)	25 (76)	42 (82)
Former smoker	229 (57)	235 (57)	218 (54)	219 (54)	8 (24)	9 (18)
Disease Severity						
mMRC dyspnea score, mean (SD)	NR	NR	NR	NR	NR	NR
Post-bronchodilator Reversibility						
Reversible	121 (30)	125 (31)	127 (32)	126 (31)	NR	NR
Non-reversible	279 (70)	282 (69)	271 (68)	276 (69)	NR	NR

COPD = chronic obstructive pulmonary disease; FF = fluticasone furoate; FF/V = fluticasone furoate + vilanterol; mMRC = Modified Medical Research Council; SD = standard deviation; V = vilanterol.
Source: Clinical Study Report for study 946.[19]

3.2.3 Interventions

In the active comparisons with fluticasone propionate plus salmeterol, the dose of fluticasone propionate plus salmeterol used was 250/50 mcg in three studies, and 500/50 mcg in study 3107. In study 5805, the dose of tiotropium was 18 mcg once daily. Fluticasone furoate plus vilanterol was administered once daily using the Ellipta device. Fluticasone propionate plus salmeterol was administered twice daily using the Accuhaler/DISKUS device, and tiotropium was administered using the HandiHaler (for a review of inhaler devices, see APPENDIX 8: SUMMARY OF DRY POWDER INHALERS). Because fluticasone furoate plus vilanterol is administered once daily, blinding was maintained by using a double-dummy design. Patients randomized to fluticasone furoate plus vilanterol were to take an active inhalation of study medication during their morning dosing from their Ellipta device and an inhalation of dummy medication (placebo) as their morning Accuhaler/DISKUS dose and as their evening dose. Those patients randomized to the fluticasone propionate plus salmeterol treatment group were to take an active dose of medication during both their morning and evening treatments from the Accuhaler/DISKUS, and a dummy placebo dose in the morning from their Ellipta device.

In the placebo-controlled study 2206, fluticasone furoate plus vilanterol 100/25 mcg and fluticasone furoate plus vilanterol 50/25 mcg once daily were the interventions, and fluticasone furoate 100 mcg, vilanterol 25 mcg, and placebo once daily were the comparators. Only data for the approved fluticasone furoate plus vilanterol 100/25 mcg dose are reported in this review. In study 2207, fluticasone furoate plus vilanterol 100/25 mcg and fluticasone furoate plus vilanterol 200/25 mcg once daily were the interventions, and comparators included fluticasone furoate 100 mcg, fluticasone furoate 200 mcg, vilanterol 25 mcg, and placebo once daily. Only the Health Canada–approved doses or relevant

components were of interest for this review, so data for the fluticasone furoate plus vilanterol 200/25 mcg and fluticasone furoate 200 mcg once-daily doses are not reported. In the vilanterol-controlled studies (study 2871 and 2970), three different doses of fluticasone furoate plus vilanterol were used as intervention, fluticasone furoate plus vilanterol 50/25 mcg and fluticasone furoate plus vilanterol 200/25 mcg once daily, in addition to the approved fluticasone furoate plus vilanterol 100/25 mcg once-daily dose. Only data for the approved fluticasone furoate plus vilanterol 100/25 mcg dose are reported in this review. The comparator was vilanterol 25 mcg once daily. In the crossover study, the three intervention groups were fluticasone furoate plus vilanterol 50/25 mcg and fluticasone furoate plus vilanterol 200/25 mcg, in addition to the approved fluticasone furoate plus vilanterol 100/25 mcg dose. Only data for the approved fluticasone furoate plus vilanterol 100/25 mcg once-daily dose are reported in this review. The comparator was placebo.

Compliance with therapy was assessed by checking the dose counter on the devices, and patients who were outside of the ≥ 80% to ≤ 120% compliance were to be re-educated on treatment compliance. The studies did not describe whether patients received instruction on how to use the devices. During the run-in, patients had to demonstrate at least 80% compliance with their run-in medications, which were placebo-containing versions of the devices used during study.

Patients in all studies were supplied with salbutamol (metered-dose inhaler or nebules) to use for symptomatic relief. Ipratropium was permitted for use during the studies, provided the patient was on a stable dose from the screening visit throughout the study; it was held for four hours prior to and during clinical visits. The use of mucolytics and oxygen was also permitted in all studies. The permitted mucolytics were not specifically listed.

A moderate COPD exacerbation required treatment with antibiotics and/or systemic corticosteroids. A mild exacerbation was self-managed, and did not require use of oral corticosteroids or antibiotics.

3.2.4 Outcomes

a) Pulmonary Function Tests

In the fluticasone propionate plus salmeterol and the tiotropium-controlled studies, the primary efficacy end point was change from baseline trough in 24-hour weighted-mean serial FEV_1 at the end of 12 weeks of treatment on treatment week 12. The weighted mean was calculated from the pre-dose FEV_1 and post-dose FEV_1 measurements at five, 15, 30, and 60 minutes and two, four, six, eight, 12, 13, 14, 16, 20, and 24 hours. Baseline trough FEV_1 was the mean of the two assessments made 30 and five minutes pre-dose on treatment day 1.

Trough FEV_1 on treatment day 169 was defined as the mean of the FEV_1 values obtained 23 and 24 hours after dosing on treatment day 168, measured at visit 12. If one of the two paired assessments was missing, then trough FEV_1 was defined as the single 23- or 24-hour assessment. For inclusion in the calculation, the 23- and 24-hour values must have been prior to the next day's dose.

b) Patient-Reported Outcomes

The CRQ-SAS included 20 items across four domains: dyspnea (five items), fatigue (four items), emotional function (seven items), and mastery (four items). When completing this instrument, participants rated their level of impairment on a seven-point scale, ranging from 1 (maximum impairment) to 7 (no impairment); thus, higher scores indicate better quality of life. A mean change of 0.5 was considered to be the minimal clinically important difference (MCID) for dyspnea, fatigue, or emotional function in patients with COPD.[37-39] The CRQ-SAS was administered before any other study

procedures were performed (including concurrent medication assessment or AE assessment, etc.) at visits during which the CRQ-SAS was performed.

The SGRQ-C is a standardized, patient-administered, COPD-specific questionnaire designed to measure the impact of COPD and its treatment on the participant's health-related quality of life. Details of the SGRQ-C are provided in Appendix 5: Validity of Outcomes. A total score as well as three subdomain scores are reported, and a decrease in score represents improvement. The subdomains are symptoms (measuring distress due to respiratory symptoms), activity (measuring the effect of disturbances on mobility and physical activity), and impacts (measuring the psychosocial impact of the disease). A change of 4 points in the SGRQ-C total score represents a clinically meaningful difference. MCIDs for the subdomains have not been established.

TABLE 19: SYMPTOM SCALES USED IN STUDIES 2206 AND 2207 (FROM CLINICAL STUDY REPORT)

	Symptom Score				
Variable	0	1	2	3	4
Breathlessness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]	
Sputum	[redacted]	[redacted]	[redacted]	[redacted]	

Symptoms

In the placebo-controlled studies (2206 and 2207), participants were instructed to complete the daily diary questions prior to performing PEF (peak expiratory flow) measurements and prior to taking study medication (i.e., single-blind or double-blind [DB]), supplemental medication (salbutamol, if applicable), and ipratropium bromide (if applicable), and to base their assessment on symptoms experienced over the last 24 hours. In vilanterol-controlled studies 2871 and 2970, patients completed a daily diary using a telephone to access the IVRS, providing information on the number of nighttime awakenings due to COPD symptoms; use of rescue medication (salbutamol), major symptoms concerning the patient's dyspnea, sputum volume, sputum purulence (colour); and minor symptoms of cough, wheeze, sore throat, colds (nasal discharge and/or nasal congestion) and fever without other cause. Patients were instructed to complete the daily diary IVRS call in the morning, prior to taking any study medication.

Exacerbations

A moderate/severe COPD exacerbation was defined in all studies as an acute worsening symptom of COPD requiring the use of any treatment other than study medication or rescue salbutamol. This

included using antibiotics, systemic corticosteroids and/or emergency treatment or hospitalization. COPD exacerbations, and the medication(s) used to treat the exacerbation, were recorded. A moderate COPD exacerbation required treatment with antibiotics and/or systemic corticosteroids, a severe COPD exacerbation required hospitalization. A mild exacerbation was self-managed and did not require use of oral corticosteroids or antibiotics.

3.2.5 Statistical Analysis

a) Active-Controlled

Study 3107 was the only one of the fluticasone propionate plus salmeterol-controlled studies that was described as a non-inferiority study, and derived a margin. The non-inferiority margin was determined to be 60 mL. The derivation is described subsequently. Although the other fluticasone propionate plus salmeterol-controlled studies appeared to use this 60 mL margin in their power calculations, none used the term non-inferiority. Study 5805 was described as being powered for superiority by the manufacturer in the Clinical Study Report (CSR).

The manufacturer presented a derivation for a non-inferiority margin of 60 mL; however, it was not entirely clear from its derivation how this value was arrived at.

Analysis of Outcomes

For the comparisons to fluticasone propionate plus salmeterol, the primary analysis used an analysis of covariance (ANCOVA) model. Covariates included baseline FEV_1, reversibility stratum, smoking status (at screening), country, and treatment. Least squares (LS) means and LS mean change from baseline for each treatment group were calculated and displayed with their associated standard errors (SE). In study 5805 (tiotropium-controlled) an analysis of covariance model with terms for baseline FEV_1, exacerbation history and reversibility stratum, smoking status (at screening), country, and treatment group was used to test statistical differences between the two treatment groups.

For the secondary outcomes, in studies 2352 and 3109, for serial FEV_1 at day 1 and day 84, the analysis used a repeated measures model with an unstructured covariance. Covariates were the same as the primary end point, but also had terms for time and treatment by time. The models used all available FEV_1 values recorded on the respective days. Missing data were not implicitly imputed in this analysis; however, all non-missing data for a patient was used within the analysis to estimate the treatment effects on the respective days. Summaries were also shown at each time point. All analyses of other efficacy end points used the modelling specified for the primary analysis (ANCOVA). In study 3107, the summary of change from baseline trough at treatment day 85 (24-hour assessment) was summarized and analyzed similarly to the analysis for the primary end point. All analyses of other efficacy end points used the modelling specified for the primary analysis (ANCOVA). In study 6974, changes from baseline for both the zero- to four-hour and the zero- to 12-hour weighted means were analyzed using an ANCOVA model with effects due to baseline FEV_1, reversibility stratum, smoking status (at screening), country, and treatment group. All analyses of other efficacy end points used the modelling specified for the primary analysis (ANCOVA). In study 5805, ANCOVA models with terms for baseline, exacerbation history and reversibility stratum, smoking status, country, and treatment group were used to test statistical differences between treatment groups for the other efficacy end points.

Multiplicity

In studies 3109 and 2352, if the primary efficacy end point was significant, then inference on the key secondary end point (time-to-onset) was also at the 5% significance level. For all secondary and other efficacy end points, pairwise treatment comparisons of fluticasone furoate plus vilanterol with

fluticasone propionate plus salmeterol were used for the intention-to-treat (ITT) population. Inferences on other end points were made at the 5% significance level without adjustment for multiplicity. In study 3107, if the primary efficacy end point was significant, then inference on the key secondary end points was done sequentially, also at the 5% significance level. First, time-to-onset was compared and, if this end point was significant, then trough FEV_1 on treatment day 85 was compared. The "other" efficacy end points were nested under the secondary end points. For all secondary and other efficacy end points, pairwise treatment comparisons of fluticasone furoate plus vilanterol with salmeterol/FP were used for the ITT population. Inferences on other end points were made at the 5% significance level without adjustment for multiplicity. In study 6974, inference on the secondary end points was made sequentially, with the end point of time-to-onset (increase of 100 mL above baseline in FEV_1) at treatment day 1 (visit 2) evaluated first. Inferences on other end points were made without adjustment for multiplicity.

In study 5805, if the primary efficacy end point was significant, then inferences on the secondary end points were to be performed using the Hochberg method to control the type I error rate, also at the 5% significance level. The "other" efficacy end points were nested under the secondary end points. Inferences on the other end points were to be made at the 5% significance level without further adjustment for multiplicity.

Sample Size

[redacted]

Analysis of Subgroups

In study 3107, subset summaries and analyses were done for the primary end point, [redacted] for the following individual criteria: reversibility, Global Initiative for Chronic Lung Disease (GOLD) category, FEV_1 category (less than 50% predicted post-bronchodilator; 50% predicted or higher post-bronchodilator), FEV_1 category (less than 60% predicted pre-bronchodilator; 60% predicted or higher pre-bronchodilator), age category (younger than 65 years; 65 years or older), hospitalization exacerbation during the prior three years (yes; no), baseline smoking status (yes; no) and cardiovascular history and risk factors. In studies 3109, 2352, 6974, and 5805, subset summaries and analyses were done for the primary and secondary efficacy end points by reversibility status, as the studies were stratified by reversibility.

b) Vilanterol-Controlled

Studies 2871 and 2970, which compared fluticasone furoate plus vilanterol to vilanterol, were superiority studies.

Analysis of Outcomes

The primary analysis of the primary efficacy end point of the annual rate of moderate and severe exacerbations was performed on the ITT population using a generalized linear model, assuming the negative binomial distribution. The response variable was the number of recorded, on-treatment, moderate and severe exacerbations experienced per patient. The explanatory variables were treatment group, smoking status at screening (stratification variable), baseline disease severity (as per cent-predicted FEV_1) and centre grouping. The model also included the logarithm of time on treatment per patient (derived from exposure start and stop) as an offset variable.

A supportive analysis was also performed on the ITT population whereby the number of moderate/severe exacerbations was analyzed using a Poisson regression model with deviance over-dispersion correction. As with the negative binomial model, the response variable was the number of recorded, on-treatment, moderate, and severe exacerbations experienced per patient. The explanatory variables were treatment group, smoking status at screening (stratification variable), baseline disease severity (as per cent-predicted FEV_1) and centre grouping. The model also included the logarithm of time on treatment per patient (derived from exposure start and stop) as an offset variable.

Using the ITT population only, separate negative binomial and Poisson models were fitted to investigate the effect of treatment by covariate interactions: (i) with the addition of an interaction term for treatment by smoking status; (ii) with the addition of an interaction term for treatment by centre grouping; and (iii) with the addition of an interaction term for treatment by per cent-predicted FEV_1. A further two models were fitted to investigate the effect of treatment by covariate interactions (iv) with the addition of a covariate of cardiovascular history and risk factors and an interaction term for treatment by cardiovascular history and risk factors, and (v) with the addition of a covariate of reversibility (yes/no) and an interaction term for treatment by reversibility. The analysis of the secondary efficacy end point of time to first moderate or severe exacerbation was performed on the ITT population using a Cox's proportional hazards model, with the "exact" method for handling ties in times of first exacerbation. Only on-treatment exacerbations falling into quarters 1 to 4 were used in the analysis.

Sample Size

Sample-size calculations were based on the primary end point, the annual rate of moderate and severe exacerbations, and on the comparison of each fluticasone furoate plus vilanterol combination treatment

group compared with the vilanterol treatment group. The annual rate of moderate and severe exacerbations in the vilanterol treatment group was assumed to be 1.4 based on estimates of 1.40 to 1.59 from previous studies of salmeterol groups of the fluticasone propionate plus salmeterol combination studies. Estimates of the dispersion parameter of 0.7 were based on previous fluticasone propionate plus salmeterol studies. A study with 390 evaluable participants per group had 90% power to detect a 25% reduction in the annual rate of moderate and severe exacerbations on a fluticasone furoate plus vilanterol combination group compared with the vilanterol group. Calculations were based on a negative binomial regression and used a two-sided 5% significance level. No adjustments in the type I error for multiplicity were made due to the step-down testing procedure employed. Patients were randomized in equal proportions to all four treatment groups and all randomized patients were considered to be evaluable, irrespective of whether they withdrew from the study prematurely. Therefore, 1,560 evaluable (randomized) participants (390 participants per treatment group) were required. Assuming a 40% screening and run-in failure rate, 2,600 participants were to be screened.

Multiplicity

To account for multiplicity across treatment comparisons and key end points, a step-down testing procedure was applied whereby inference for the primary efficacy end point for the fluticasone furoate plus vilanterol 100/25 combination dose versus vilanterol was dependent upon statistical significance at the 5% level, having first been achieved for the primary efficacy end points for the fluticasone furoate plus vilanterol 200/25 versus vilanterol. Similarly, inference for the primary efficacy end point for the fluticasone furoate plus vilanterol 50/25 versus vilanterol was dependent upon statistical significance having first been achieved for the primary efficacy end point for the fluticasone furoate plus vilanterol 100/25 versus vilanterol. For a given fluticasone furoate plus vilanterol combination dose, the secondary end points were nested under the primary end point. Secondary efficacy end points were (in order): time to first moderate or severe exacerbation, the annual rate of exacerbations requiring treatment with systemic or oral corticosteroids, and trough FEV_1 at 52 weeks. Hence, in order to make inferences on the secondary end points at a given strength, statistical significance at the 5% level had to have been demonstrated for the primary efficacy end point for that combination strength. For each strength of fluticasone furoate plus vilanterol, "other" efficacy end points were nested under the secondary end points; the latter acted as gatekeeper for inference for the "other" end points. For a given combination dose, inference for the other end points was therefore contingent on the comparison of fluticasone furoate plus vilanterol versus vilanterol being statistically significant for the primary and all three secondary end points (subject to the step-down testing rule described previously).

No further multiplicity adjustments were applied.

The pattern of missing data due to study withdrawals was examined using Kaplan-Meier plots of time to withdrawal and tabulation of reasons for withdrawal by time. To further examine any impact of withdrawals, a supporting summary of the annual rate of moderate and severe exacerbations was performed on intervals of less than one year. Summary statistics by treatment group for moderate and severe annual exacerbation rates using only data from the first quarter, from quarters one and two, from quarters one to three, and from the whole year (quarters one to four) were given, where moderate and severe exacerbation rates were imputed for participants who did not reach the end of each given time period.

Subgroups

No formal statistical analysis of subgroups of the populations was performed.

c) Placebo-Controlled

In the placebo-controlled studies 2206/2207, for change from baseline trough FEV_1 on day 169, the primary treatment comparisons of interest were:

- Vilanterol versus placebo (24-hour duration of vilanterol)
- Each fluticasone furoate plus vilanterol dose versus placebo (efficacy of a combination dose on end of dosing interval lung function)
- Each fluticasone furoate plus vilanterol dose versus vilanterol alone (contribution of fluticasone furoate to the combination).

However, the following comparisons were also provided as supportive for describing the contribution of the mono-components to the combination:

- Each fluticasone furoate dose versus placebo
- Each fluticasone furoate plus vilanterol dose versus the relevant fluticasone furoate dose alone.

All primary comparisons were performed at the 5% significance level and used the ITT population.

The primary analysis was performed using mixed model repeated measures (MMRM) and had covariates of baseline FEV_1, smoking status (stratum), day, centre grouping, treatment, day by baseline interaction and day by treatment interaction, where day is nominal. The model used all available zero- to four-hour weighted-mean FEV_1 values recorded on days 1, 14, 56, 84, and 168. Missing data were not directly imputed in this analysis; however, all non-missing data for a participant were used within the analysis to estimate the treatment effect for zero- to four-hour weighted-mean FEV_1 on day 168. An additional analysis was also performed for the ITT population, imputing missing data using last observation carried forward (LOCF) for zero- to four-hour weighted-mean FEV_1 post-dose on day 168. For this analysis, where the end point was missing, the last non-missing post-baseline weighted mean was used instead. The LOCF analysis was performed using an ANCOVA model with covariates of baseline, smoking status, centre grouping, and treatment.

Sample Size

Sample-size calculations were based on the co-primary end points. The sample-size calculations used an estimate of residual SD of 210 mL, which was based on the phase IIb study of vilanterol in COPD participants (study B2C111045) and previous studies in COPD participants with the fluticasone propionate plus salmeterol combination. A study with 146 evaluable participants per group has a 90% power to detect an 80 mL difference between fluticasone furoate plus vilanterol and vilanterol in trough FEV_1 on day 169, a treatment difference considered appropriate for this comparison. A two-sample t-test and two-sided 5% significance level was used in these calculations. A 100 mL difference was considered appropriate for comparisons of vilanterol versus placebo and fluticasone furoate plus vilanterol versus placebo for both trough FEV_1 and zero- to four-hour weighted-mean FEV_1 and of fluticasone furoate plus vilanterol versus fluticasone furoate for zero- to four-hour weighted-mean FEV_1. A study with 146 evaluable participants per group has 98% power to detect a treatment difference of 100 mL for these comparisons. To allow for an estimated 27% withdrawal rate, 200 participants were to be randomized to each treatment group.

Multiplicity

To account for multiplicity across treatment comparisons and key end points, a step-down testing procedure was applied whereby inference for a test in the pre-defined hierarchy was dependent upon statistical significance having been achieved for the previous tests in the hierarchy.

Subgroups
No formal statistical analysis of subgroups of the populations was performed.

d) Crossover
Study 946 was a superiority study.

The primary comparisons of interest were the pairwise comparison of each dose regimen of fluticasone furoate plus vilanterol with placebo for the primary end point, zero- to 24-hour weighted-mean FEV_1 over period days 28 to 29, with inference restricted by the step-down multiplicity strategy. Pairwise comparisons of each dose regimen of fluticasone furoate plus vilanterol with placebo were performed for all secondary efficacy end points and for analysis of peak FEV_1.

As the study was a crossover design, period was included as a covariate in all analysis models. Additionally, period baseline and mean baseline were included as covariates in all relevant analysis models where available.

Sample-size calculations were based on the primary end point, zero- to 24-hour weighted-mean FEV_1 over period days 28 to 29 for the comparison of each fluticasone furoate plus vilanterol treatment (50/25 mcg, 100/25 mcg, 200/25 mcg) compared with placebo. Using an incomplete block crossover design (with all patients receiving placebo and two of three strengths of fluticasone furoate plus vilanterol), it was estimated that a total of 27 patients with evaluable data from all three periods would provide 90% power to detect a difference of 130 mL between a fluticasone furoate plus vilanterol dose and placebo in zero- to 24-hour weighted-mean FEV_1 at the two-sided 5% significance level. This assumed a SD of 123 mL. No adjustments in the type I error rate for multiplicity were made due to the step-down closed testing procedure employed. Comparisons were not performed between dose regimens of fluticasone furoate plus vilanterol.

To account for multiplicity across treatment comparisons for the primary efficacy end point, a step-down closed testing procedure was applied whereby inference for the fluticasone furoate plus vilanterol 100/25 mcg combination dose versus placebo was dependent upon statistical significance having first been achieved for fluticasone furoate plus vilanterol 200/25 mcg versus placebo. Similarly, inference for fluticasone furoate plus vilanterol 50/25 mcg versus placebo was dependent upon statistical significance having first been achieved for the fluticasone furoate plus vilanterol 100/25 mcg versus placebo.

e) Analysis Populations
The ITT population was the population of primary interest for all efficacy and safety end points in all studies.

The ITT population was defined in all studies as all participants who had been randomized to and received at least one dose of randomized DB study medication in the treatment period.

The per-protocol population in all studies comprised all participants in the ITT population not identified as full protocol deviators with respect to criteria that were considered to affect the primary efficacy analysis.

3.3 Patient Disposition
In the active-controlled studies involving fluticasone furoate plus vilanterol versus fluticasone propionate plus salmeterol, there were no clear differences in rate of withdrawals between groups, and

the withdrawal rate ranged between 6% and 11% within groups across studies. In the comparison with tiotropium (study 5805), there were numerically fewer withdrawals with fluticasone furoate plus vilanterol than with tiotropium (6% versus 12% of patients withdrew).

Conversely, withdrawal rates in the placebo-controlled studies 2206/2207 were high, often around 30%. Note that these were 24-week studies, and the active-controlled studies aforementioned were 12 weeks in duration. There were some differences in withdrawal rates between groups in each study, notable among them being the fluticasone furoate plus vilanterol withdrawals of 27% versus 33% with placebo in study 2206, while in study 2207 both the fluticasone furoate plus vilanterol and placebo groups had withdrawal rates of 29%, higher than withdrawals with the fluticasone furoate component (24%) and the vilanterol component (21%).

[redacted]

The most common reasons for withdrawal across studies were due to AE and lack of efficacy.

The withdrawal rate in the crossover study was low (6% in each of the fluticasone furoate plus vilanterol and placebo groups) and there was no difference between groups.

TABLE 20: PATIENT DISPOSITION: ACTIVE (FLUTICASONE PROPIONATE PLUS SALMETEROL)-CONTROLLED

	Study 3107		Study 6974		Study 3109		Study 2352	
	FF/V 100/25	FP/S 500/50	FF/V 100/25	FP/S 250/50	FF/V 100/25	FP/S 250/50	FF/V 100/25	FP/S 250/50
Screened, N	702		993		733		739	
Randomized, N (%)	266	262	412	416	260	259	259	252
Discontinued study, N (%)	23 (9)	16 (6)	46 (11)	45 (11)	21 (8)	24 (9)	20 (8)	15 (6)
Adverse event	6 (2)	3 (1)	14 (3)	16 (4)	4 (2)	8 (3)	5 (2)	1 (< 1)
Lack of efficacy	3 (1)	2 (< 1)	4 (< 1)	4 (< 1)	2 (< 1)	0	6 (2)	2 (< 1)
Exacerbation								
Protocol deviation	[redacted]							
Lost to follow-up								
Investigator discretion								
Patient withdrew consent								
ITT, N	266	262	412	416	260	259	259	252
Per-protocol, N	[redacted]							

FF/V = fluticasone furoate + vilanterol; FP/S = fluticasone propionate + salmeterol; FVC = forced vital capacity; ITT = intention-to-treat; V = vilanterol.
Source: Clinical Study Reports for study 3107, [10] study 6974, [11] study 3109, [12] and study 2352.[13]

TABLE 21: PATIENT DISPOSITION: ACTIVE (TIOTROPIUM)-CONTROLLED

	Study 5805	
	FF/V 100/25	**TIO 18**
Screened, N	890	
Randomized, N (%)	310	313
Discontinued study, N (%)	19 (6)	39 (12)
Adverse event	6 (2)	12 (4)
Lack of efficacy	4 (1)	11 (4)
Exacerbation	4 (1)	9 (3)
Protocol deviation	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Investigator discretion	[redacted]	[redacted]
Patient withdrew consent	[redacted]	[redacted]
ITT, N	310	313
Per-protocol, N	292 (94)	289 (92)

FF/V = fluticasone furoate + vilanterol; ITT = intention-to-treat; TIO = tiotropium.
Source: Clinical Study Report for study 5805.[14]

TABLE 22: PATIENT DISPOSITION: PLACEBO-CONTROLLED

	Study 2206				Study 2207			
	FF/V 100/25	**PLA**	**FF 100**	**V25**	**FF/V 100/25**	**PLA**	**FF 100**	**V25**
Screened, N	1804				1909			
Randomized, N (%)	206	207	206	205	204	205	204	203
Discontinued study, N (%)	55 (27)	69 (33)	61 (30)	63 (31)	60 (29)	59 (29)	49 (24)	42 (21)
Adverse event	14 (7)	15 (7)	23 (11)	24 (12)	17 (8)	18 (9)	12 (6)	15 (7)
Lack of efficacy	12 (6)	20 (10)	18 (9)	15 (7)	8 (4)	12 (6)	5 (2)	11 (5)
Exacerbation	12 (6)	17 (8)	16 (8)	13 (6)	7 (3)	12 (6)	2 (< 1)	11 (5)
Protocol deviation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stopping criteria reached	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigator discretion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient withdrew consent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ITT, N	206	207	206	205	204	205	204	203
Per-protocol, N	197 (96)	196 (95)	204 (> 99)	191 (93)	193 (95)	198 (97)	193 (95)	191 (94)

FF = fluticasone furoate; FF/V = fluticasone furoate + vilanterol; ITT = intention-to-treat; PLA = placebo; V = vilanterol.
Source: Clinical Study Reports for studies 2206[15] and 2207.[16]

TABLE 23: PATIENT DISPOSITION: VILANTEROL-CONTROLLED

	Study 2871		Study 2970	
	FF/V 100/25	V25	FF/V 100/25	V25
Screened, N	2631		2635	
Randomized, N (%)	403	409	403	409
Discontinued study, N (%)	91 (23)	115 (28)	112 (28)	125 (31)
Adverse event	29 (7)	22 (5)	35 (9)	25 (6)
Lack of efficacy	11 (3)	24 (6)	16 (4)	35 (9)
Exacerbation	4 (< 1)	15 (4)	9 (2)	20 (5)
Protocol deviation	[redacted]	[redacted]	[redacted]	[redacted]
Stopping criteria reached	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]
Investigator discretion	[redacted]	[redacted]	[redacted]	[redacted]
Patient withdrew consent	[redacted]	[redacted]	[redacted]	[redacted]
Study closed/terminated	[redacted]	[redacted]	[redacted]	[redacted]
ITT, N	403	409	403	409
Per-protocol, N	[redacted]	[redacted]	[redacted]	[redacted]

FF/V = fluticasone furoate + vilanterol; ITT = intention-to-treat; V = vilanterol.
Source: Clinical Study Reports for study 2871[17] and study 2970.[18]

TABLE 24: PATIENT DISPOSITION — CROSSOVER

	Study 946	
	FF/V 100/25	PLACEBO
Screened, N	87	
Randomized, N (%)	33	51
Discontinued, N (%)	2 (6)	3 (6)
Adverse event	0	0
Lack of efficacy	0	0
Exacerbation	0	0
Protocol deviation	1	0
Stopping criteria reached	0	0
Lost to follow-up	1	1
Investigator discretion	0	0
Patient withdrew consent	0	2
Study closed/terminated	0	0
ITT, N	33	51
Per-protocol, N	29 (88)	48 (94)

FF/V = fluticasone furoate + vilanterol; ITT = intention-to-treat.
Source: Clinical Study Report for study 946.[19]

3.4 Exposure to Study Treatments

[redacted] There were some differences in exposure between groups in the placebo-controlled studies, with a range of 132.0 to 148.7 days; however, there was no consistent difference in exposure

between groups across studies. [redacted]

Exposure to concomitant COPD and non-COPD medications is summarized in APPENDIX 5: DETAILED OUTCOME DATA. [redacted] with no obvious differences between groups within each study. [redacted] The most common concomitant medications in the placebo-controlled studies (study 2206 and 2207) were again the short-acting anticholinergics (SAAC), with a range of 17% to 30% across groups across studies. In study 2207, use of SAAC was similar between groups, while in study 2206, use was highest with placebo, 30%, compared with 22% with fluticasone furoate plus vilanterol and 20% with vilanterol. In the vilanterol-controlled studies (study 2871 and 2970), use of concomitant medications associated with exacerbations was reported. Antibiotics were the most common medication for moderate exacerbations (approximately 34% for fluticasone furoate plus vilanterol versus 40% with vilanterol across studies) while systemic corticosteroids were the most common for severe exacerbations (7% versus 6%, respectively). Across all studies, the most common non-COPD medications were for the cardiovascular and nervous systems.

3.5 Critical Appraisal

3.5.1 Internal Validity

Randomization was performed using an IVRS and appropriate measures appear to have been taken to maintain allocation concealment. Randomization was stratified in the active-controlled studies by baseline bronchodilator reversibility, an acknowledgement of the potential importance of this baseline characteristic to fluticasone furoate plus vilanterol responses.

The included studies used a modified ITT (patients randomized and treated) rather than a true ITT population (all patients randomized to a given intervention, regardless of whether they received study drug). The modified ITT more closely resembles what is typically described as a safety population (randomized and treated); however, because there were no differences between the randomized and ITT populations, this is not of concern.

Adjustments were made for multiple testing for at least the primary and many secondary outcomes and, in many cases, tertiary/other outcomes as well. It is not clear whether adjustments were made for subgroup analyses.

There was no detailed description of how patients were trained on use of the devices (Ellipta or comparators) provided in the CSRs. Patients practiced using the devices during the run-in period, but it was unclear what amount of training in the use of the devices was provided to the patients. Compliance was tracked, and patients who were above or below a certain threshold for compliance were reminded of the importance of adhering to their regimen. However, compliance was only assessed using a dose counter, which simply indicates how many doses are dispensed, versus how many doses are delivered accurately to the patient. One way to more accurately assess compliance with inhaler therapy is to have an observer watch patients deliver a dose to themselves and provide commentary and suggestions for improvement.

The included studies were DB, considered the gold standard for randomized controlled trial design. The challenge in some studies was that fluticasone furoate plus vilanterol, which is administered once daily, was compared with fluticasone propionate plus salmeterol, which is administered twice daily. The investigators addressed this by using a double-dummy design, in which the second fluticasone furoate plus vilanterol dose was administered using a placebo inhaler. This is a standard method for maintaining blinding when you have two different regimens being compared in this way. However, the added complication in the case of an inhaler device is that the patient may be able to detect a difference in formulation between fluticasone furoate plus vilanterol and placebo inhalers, as some of the drug will be deposited in the oral cavity. If used correctly, patients may not taste the powder dispensed from a dry powder inhaler, as most would be deposited in the airways; however, it is not known whether patients were using the device correctly, and it is not clear whether there were differences in taste between the placebo powder and the active interventions. Although knowledge of treatment assignment is less likely to bias hard clinical outcomes such as mortality, it could certainly bias patient-reported outcomes such as symptoms and quality of life.

Patients in the included trials were all required to complete a two-week run-in period, where they were typically assigned to placebo versions of the inhaler devices they would be using in the study. This also provided a washout period. (The vilanterol-controlled studies used fluticasone propionate plus salmeterol during run-in, [redacted].) It is not clear that the appropriate washout period, particularly for an ICS, has been established. The washout might also bias results in the placebo-controlled trials. Patients who were on an ICS/LABA combination, or its components, prior to enrolling in the trial would have to discontinue these therapies for the washout period. Patients who are reintroduced to ICS/LABA or one of its components may experience an exaggerated response when reintroduced to these therapies, and patients who are assigned to placebo may experience negative effects from discontinuation of medications that might have been providing them with a therapeutic benefit. In the placebo-controlled studies in this review, between 31% and 38% of patients were on a LABA prior to study enrolment, and 18% to 27% were on an ICS, across the various groups. In the placebo group, specifically, the proportions were 33% on LABA and 23% on ICS. The effects of study washout in COPD are further reviewed in Suissa 2014, where the authors suggest that the washout period, particularly in patients who will be taking study medications of the same class as the ones they discontinued, should be considered as part of the intervention in that study.[40]

Although a non-inferiority margin was derived and appears to have been applied to all of the fluticasone propionate plus salmeterol-controlled studies, this was only clearly stated in one of the studies (study 3107), and it was not clear from the conclusions in any of the CSRs that a non-inferiority design had been employed or that non-inferiority had been established (which was the case). The same was true of study 5805, versus tiotropium, which was described by the manufacturer as powered for superiority, but superiority was not alluded to in the study conclusions. The data from study 5805 would appear to suggest that superiority was not established.

Study 946 employed a crossover design, where patients were treated in each treatment period for four weeks, followed by a two-week washout before being crossed over to the next treatment. It is not clear what the optimal washout period is for patients taking fluticasone furoate plus vilanterol, particularly the ICS component, as the biological half-life of a corticosteroid is longer than its elimination half-life.

3.5.2 External Validity

With the possible exception of the vilanterol-controlled studies, with a treatment duration of one year, the included studies were of insufficient duration to assess clinically relevant efficacy outcomes such as

mortality and COPD-related mortality, and exacerbations. This is particularly the case with the active-controlled studies, which were all of 12 weeks' duration. Limited treatment duration may also impact the assessment of harms, as notable harms such as pneumonia occurred too infrequently in the active-controlled studies to permit comparison between fluticasone furoate plus vilanterol and key comparators like fluticasone propionate plus salmeterol. Higher rates of pneumonia in the 52-week studies allowed for a numerical comparison between fluticasone furoate plus vilanterol and vilanterol groups. Analyses of harms should also be made against other relevant comparators such as budesonide/formoterol.

The included studies enrolled patients who were at least 40 years of age, slightly younger than one would expect in a COPD population. The average age of patients was typically early 60s, while an Ontario study found the majority of their 600,000 COPD patients were older than 65 years.[41] There were other signs of a relatively young population for COPD, including the high proportion of current versus former smokers. Thus, it is possible that the results of the included studies might not completely reflect the demographics of COPD in Canada.

Across the included studies, approximately 30% of patients exhibited post-bronchodilator reversibility at baseline. These patients likely have asthma in addition to COPD, as it is in asthma that one would see this post-bronchodilator reversibility. The studies included in this review did not exclude patients with a prior history of asthma, and the two conditions often do coexist; however, it is questionable whether 30% of patients exhibiting asthma symptoms is reflective of the general population of COPD patients, according to the clinical expert involved in the review. The significance of patients with underlying asthma is that they are more likely to respond to an ICS/LABA combination. Concern over this potential source of bias is reduced somewhat by the fact that the active-comparator studies stratified randomization based on post-bronchodilator reversibility.

None of the included studies included the budesonide plus formoterol (Symbicort Turbuhaler), the other ICS/LABA combination approved for COPD in Canada. Although there is a considerable body of short-term data evaluating fluticasone furoate plus vilanterol versus fluticasone propionate plus salmeterol, the absence of trials comparing fluticasone furoate plus vilanterol to budesonide plus formoterol represents a gap in knowledge, as fluticasone propionate plus salmeterol and budesonide plus formoterol have some differences, perhaps most notable being a much faster onset LABA in formoterol, which may mean that budesonide plus formoterol is able to provide enhanced symptomatic relief in certain patients versus fluticasone propionate plus salmeterol. A recently published cohort analysis of 160,000 COPD patients also reported a lower risk of pneumonia in patients treated with budesonide versus fluticasone propionate, again suggesting that budesonide plus formoterol is a relevant comparator.[42]

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol (section 2.2, Table 8) are presented here. The efficacy data are presented in Table 25 through Table 30. See APPENDIX 5: DETAILED OUTCOME DATA for detailed efficacy data.

3.6.1 Mortality

a) Active-Controlled

[redacted]

[redacted]

b) Placebo-Controlled

[redacted]

c) Vilanterol-Controlled

[redacted]

d) Crossover

Deaths were not reported.

3.6.2 Mortality Due to COPD

In the vilanterol-controlled studies, there were two deaths due to COPD with each of fluticasone furoate plus vilanterol and vilanterol. There were no other deaths due to COPD in any of the included studies.

3.6.3 Health Care Resource Utilization

a) Active-Controlled

Detailed exacerbation outcomes data were available in studies 3107 and 6974 and, in study 3107, two out of six fluticasone furoate plus vilanterol exacerbations resulted in hospitalization, versus one out of seven fluticasone propionate plus salmeterol exacerbations. In study 6974, six of 21 fluticasone furoate plus vilanterol exacerbations and eight of 19 fluticasone propionate plus salmeterol exacerbations resulted in hospitalization. No statistical analysis was provided. A majority of patients received oral steroids to resolve their exacerbation, and many were treated with antibiotics (between 50% and 100% of exacerbations received antibiotics).

In study 5805, three of eight exacerbations in the fluticasone furoate plus vilanterol group resulted in hospitalization, versus one of 11 with tiotropium. The majority of exacerbations were managed with oral steroids (88% versus 82%, respectively) and 50% of exacerbations in the fluticasone furoate plus vilanterol group and 82% of exacerbations in the tiotropium group received antibiotics.

b) Placebo-Controlled

In patients with severe exacerbations, there were a similar number of in-patient ward hospital days for fluticasone furoate plus vilanterol versus placebo (33 each) in study 2206. There were 20 ward hospital days with fluticasone furoate and 45 days with vilanterol monotherapy. No statistical analyses were provided. There were very few ICU hospitalization days.

There were 55 ward hospitalization days with fluticasone furoate plus vilanterol and 64 days with placebo in study 2207; however, there were numerically more ICU hospitalization days with fluticasone furoate plus vilanterol than with placebo (30 versus 12 days).

c) Vilanterol-Controlled

With respect to ICU hospitalizations due to severe exacerbations, there were numerically fewer days in the ICU for fluticasone furoate plus vilanterol patients than with vilanterol in both study 2871 (19 versus 131 days) and study 2970 (22 versus 35 days). In study 2871, there were numerically fewer ward

hospitalizations due to severe exacerbations with fluticasone furoate plus vilanterol than with vilanterol (202 versus 245 days), but numerically more with fluticasone furoate plus vilanterol than with vilanterol in study 2970 (189 versus 148 days). No statistical analyses were provided.

d) Crossover

No hospitalization data were reported for study 946.

3.6.4 Symptoms

a) Active-Controlled

Symptom scores based on diary entries were not reported for the fluticasone propionate plus salmeterol-controlled studies. [redacted]

b) Placebo-Controlled

Symptoms scores assessed were based on diaries for cough, sputum, and breathlessness, and each of these was statistically significantly improved for fluticasone furoate plus vilanterol versus placebo for both studies 2206 and 2207. In study 2206, the between-group difference in LS mean (weeks 1–24) for cough was –0.20 ([95% CI: –0.29 to –0.10], $P < 0.001$), and in study 2207 it was –0.13 ([–0.22 to –0.03], $P = 0.008$). For sputum, in study 2206 it was –0.11 ([–0.20 to –0.02], $P = 0.021$) and in study 2207 it was –0.14 ([–0.23 to –0.05], $P = 0.002$). For breathlessness, in study 2206 it was –0.31 ([–0.43 to –0.19], $P < 0.001$) and in study 2207 it was –0.31 ([–0.42 to –0.20], $P < 0.001$).

c) Vilanterol-Controlled

Dyspnea scores (by IVRS diary) for weeks 1–52 were statistically significantly improved for fluticasone furoate plus vilanterol versus vilanterol in each of studies 2871 (LS mean, between-group difference [95% CI]: –0.08 [–0.14 to –0.01], $P = 0.019$) and 2970 (–0.11 [–0.17 to –0.05], $P < 0.001$). These studies also reported the proportion of 24-hour periods without increased sputum; however, statistical analysis was not presented.

d) Crossover

Symptoms were not reported in this study.

3.6.5 Quality of Life

a) Active-Controlled

Quality of life was assessed using the SGRQ in studies 3107 and [redacted]. A decrease in score represents improvement. There was no difference in change from baseline in total score when fluticasone furoate plus vilanterol was compared with fluticasone propionate plus salmeterol or [redacted]. In study 3107, the reduction from baseline of –4.78 for fluticasone furoate plus vilanterol exceeded the MCID of 4.0; [redacted]. The MCIDs for the SGRQ are reported in APPENDIX 6: VALIDITY OF OUTCOME MEASURES.

[redacted]

b) Placebo-Controlled

Quality of life was assessed using the CRQ-SAS instrument in the placebo-controlled studies 2206 and 2207. The CRQ-SAS dyspnea subscale was statistically significantly improved from baseline for fluticasone furoate plus vilanterol versus placebo in both study 2206 (mean between-group difference [95% CI]: 0.30 [0.06 to 0.54], *P* = 0.014) and study 2207 (mean between-group difference [95% CI]: 0.24 [0.02 to 0.46], *P* = 0.029). The individual components of fluticasone furoate plus vilanterol, fluticasone furoate, and vilanterol, did not improve scores versus placebo. Similarly, the CRQ-SAS total score was statistically significantly improved for fluticasone furoate plus vilanterol versus placebo in both study 2206 (mean between-group difference [95% CI]: 0.25 [0.07 to 0.42], *P* = 0.005) and study 2207 (mean between-group difference [95% CI]: 0.21 [0.04 to 0.38], *P* = 0.015), and the individual components of fluticasone furoate plus vilanterol failed to demonstrate improvement versus placebo.

Quality of life was not reported in the vilanterol-controlled studies or in the crossover study.

3.6.6 Exacerbations

a) Active-Controlled

There were a similar number of exacerbations between fluticasone furoate plus vilanterol and fluticasone propionate plus salmeterol groups in the two studies reporting (study 3107: 6 versus 7 exacerbations, respectively, [redacted] No statistical analyses were provided in any of these studies. All of the exacerbations were reported as having resolved, and the majority were resolved using oral steroids. [redacted] There was no obvious pattern of exacerbations leading to hospitalization, and the numbers were too small to draw any conclusions.

b) Placebo-Controlled

Exacerbations were reported in both studies 2206 and 2207. The proportion of patients with an exacerbation in study 2206 was 9% of fluticasone furoate plus vilanterol-treated patients, and 10% with placebo and, in study 2207, the proportions were 6% and 10%, respectively. No statistical analyses were provided.

c) Vilanterol-Controlled

The annualized rate of moderate/severe exacerbations was the primary outcome for studies 2871 and 2970. In both studies 2871 and 2970, the annualized rate of moderate/severe exacerbations was statistically significantly lower for fluticasone furoate plus vilanterol versus vilanterol (study 2871, LS mean of 0.70 versus 1.05, *P* < 0.001; study 2970, LS mean of 0.90 versus 1.14, *P* = 0.024). [redacted] The time to first moderate/severe exacerbation was also reported as a hazard ratio (HR) for each study, and these were statistically improved for fluticasone furoate plus vilanterol versus vilanterol in study 2871 (HR [95% CI]: 0.72 [0.59 to 0.89], *P* = 0.042) and study 2970 (0.80 [0.66 to 0.99], *P* = 0.036).

[redacted]

[redacted]

d) Crossover

Exacerbations were not reported in study 946.

3.6.7 Spirometry

a) Active-controlled

Change from baseline trough in 24-hour weighted-mean FEV_1 on treatment day 84 was the primary outcome of all active-controlled studies. For FEV_1 weighted mean over 0 to 24 hours, there was no statistically significant difference in LS mean change from baseline between fluticasone furoate plus vilanterol and fluticasone propionate plus salmeterol in three of four studies. The exception was study 3109, where the fluticasone furoate plus vilanterol group had an increase of 0.174 versus 0.094 L with fluticasone propionate plus salmeterol ($P < 0.001$). There was no statistically significant difference for this outcome when compared with tiotropium in study 5805.

In the two studies (3107 and 6974) reporting LS mean change from baseline for trough FEV_1 there was no statistically significant difference between fluticasone furoate plus vilanterol and fluticasone propionate plus salmeterol or between fluticasone furoate plus vilanterol and tiotropium.

[redacted]

b) Placebo-Controlled

In studies 2206 and 2007, both the FEV_1 (0 to 4 hours) and trough FEV_1 were statistically significantly improved for fluticasone furoate plus vilanterol versus placebo. These were the co-primary outcomes of these studies.

For trough FEV_1, the between-group difference in mean change from baseline (95% CI) was 0.115 L ([0.060 to 0.169], $P < 0.001$) in study 2206 and 0.145 L ([0.095 to 0.196], $P < 0.001$) in study 2207. Looking at individual components of fluticasone furoate plus vilanterol, improvements from baseline were numerically greater for vilanterol (study 2206: mean ± SD change from baseline of 0.111 ± 0.256 L; study 2207: 0.109 ± 0.254 L) than for fluticasone furoate (study 2206: 0.089 ± 0.284 L; study 2207: 0.034 ± 0.241 L).

For FEV_1 (0 to 4 hours), in study 2206 the between-group difference in mean change from baseline (95% CI) was 0.173 ([0.123 to 0.224], $P < 0.001$) for fluticasone furoate plus vilanterol versus placebo, and in study 2207 it was 0.214 ([0.161 to 0.266], $P < 0.001$) for fluticasone furoate plus vilanterol versus placebo.

c) Vilanterol-Controlled

FEV_1 (zero to four hours or zero to 24 hours) was not reported in either study 2871 or 2970. Trough FEV_1 was statistically significantly improved for fluticasone furoate plus vilanterol versus vilanterol alone in study 2871 (between-group difference of mean change from baseline [95% CI]: 0.058 L [0.027 to 0.090], $P < 0.001$) but not in study 2970.

d) Crossover

LS mean change from baseline to four weeks for FEV_1 (0 to 24 hours) and trough FEV_1 were both statistically significantly improved for fluticasone furoate plus vilanterol versus placebo in study 946. For FEV_1 (zero to 24 hours), the between-group difference in LS mean change from baseline (95% CI (was 0.220 ([0.165 to 0.275], $P < 0.001$) and for trough FEV_1 it was 0.177 ([0.097 to 0.257], $P < 0.001$).

e) Subgroups

[redacted] (see Table 45 in APPENDIX 5: DETAILED OUTCOME DATA). [redacted]

For the vilanterol-controlled studies (see Table 45 in Appendix 4), subgroup data were available for the primary outcome of those studies, the annualized rate of moderate/severe exacerbations. Subgroups by baseline reversibility status was only reported in study 2871, and the direction of effect was similar in both patients exhibiting bronchodilator reversibility at baseline and those not exhibiting reversibility. Baseline smoking status (current or former smoker) also did not appear to impact exacerbation rates. No interaction *P* values were reported. Trough FEV_1 responses (Table 46 in Appendix 4) were also reported by reversibility and smoking status, and again there were no clear trends with respect to the impact of baseline reversibility (study 2970) or smoking status (study 2871).

In the placebo-controlled studies (Table 47 in Appendix 4), trough FEV_1 responses were available by subgroups. Responses by baseline reversibility status were only reported for study 2206, and again the direction of response was similar between patients exhibiting baseline reversibility and those not. No interaction *P* values were reported. [redacted]

3.6.7 Other Efficacy Outcomes

[redacted] Rescue medication use was also reduced versus placebo in both studies 2206 and 2207, and these differences were statistically significant for fluticasone furoate plus vilanterol versus placebo, and also for the components, vilanterol in both studies, and fluticasone furoate in study 2206 but not study 2207, versus placebo. In the vilanterol-controlled studies, there was a statistically significant reduction in rescue medication use for fluticasone furoate plus vilanterol versus vilanterol in study 2970 but not study 2871.

Patient adherence was around 98%, in all groups, and there were no obvious differences between groups in any study.

TABLE 25: KEY EFFICACY OUTCOMES ACTIVE-CONTROLLED (FLUTICASONE PROPIONATE PLUS SALMETEROL)

	Study 3107		Study 6974	
	FF/V 100/25 N = 266	FP/S 500/50 N = 262	FF/V 100/25 N = 412	FP/S 250/50 N = 416
FEV_1, 0- to 24-Hour Weighted Mean				
LS mean at day 84, L	1.417 (0.015)	1.40 (0.015)	1.523 (0.012)	1.497 (0.012)
LS mean change from baseline (SE) day 84, L	0.130 (0.015)	0.108 (0.015)	0.168 (0.012)	0.142 (0.012)
LS MD (95% CI)	0.022 (–0.018 to 0.063)		0.025 (–0.008 to 0.059)	
P value	*P* = 0.282		*P* = 0.137	
Trough FEV_1				
LS mean (SE) baseline, L	1.403 (0.016)	1.380 (0.015)	1.497 (0.0126)	1.467 (0.0125)
LS mean change (SE), L	0.111 (0.016)	0.088 (0.015)	0.151 (0.0126)	0.121 (0.0125)
LS MD (95% CI)	0.023 (–0.020 to 0.066)		0.030 (–0.005 to 0.065)	
P value	*P* = 0.294		*P* = 0.089	
Inspiratory Capacity, Pre-Dose				
LS mean baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change at week 12 (SE), L	[redacted]	[redacted]	[redacted]	[redacted]
LS MD (95% CI)	[redacted]			
P value	[redacted]			
SGRQ Total Score				
LS mean (SE) change, week 12	[redacted]	[redacted]	[redacted]	[redacted]
LS MD (95% CI)	[redacted]		[redacted]	[redacted]
P value	[redacted]			
EQ-5D VAS				
LS mean (SE) change, week 12	[redacted]	[redacted]	[redacted]	[redacted]
LS MD (95% CI)	[redacted]		[redacted]	[redacted]
P value	[redacted]			
Symptoms				
Mean (SD) change from baseline, weeks 1 to 12	NR	NR	NR	NR
Between-group difference of change from baseline (95% CI)	NR	NR	NR	NR
P value				
Deaths (All-Cause)				
On treatment, n (%)	1	0	1	3
During follow-up, n (%)				
Deaths, COPD				

	Study 3107		Study 6974	
	FF/V 100/25 N = 266	FP/S 500/50 N = 262	FF/V 100/25 N = 412	FP/S 250/50 N = 416
On treatment, n (%)	0	0	0	0
Exacerbations				
Total	6	7	[redacted]	[redacted]
Resolved	6	7	[redacted]	[redacted]
Resolved with oral CS	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalized	[redacted]	[redacted]	[redacted]	[redacted]
Treated with antibiotics	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawn due to exacerbation	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; COPD = chronic obstructive pulmonary disease; CS = corticosteroids; EQ-5D VAS = EuroQol 5-Dimensions questionnaire visual analogue scale; FEV_1 = forced expiratory volume in 1 second; FF/V = fluticasone furoate + vilanterol; FP/S = fluticasone propionate + salmeterol; LS = least squares; MD = mean difference; NR = not reported; SD = standard deviation; SE = standard error; SGRQ = St. George's Respiratory Questionnaire.
Source: Clinical Study Reports for study 3107, [10] study 6974.[11]

TABLE 26: KEY EFFICACY OUTCOMES ACTIVE-CONTROLLED (FLUTICASONE PROPIONATE PLUS SALMETEROL)

	Study 3109		Study 2352	
	FF/V 100/25 N = 260	FP/S 250/50 N = 259	FF/V 100/25 N = 259	FP/S 250/50 N = 252
FEV_1, 0- to 24-Hours Weighted Mean				
LS mean at day 84 (L)	1.513 (0.015)	1.433 (0.016)	1.475 (0.018)	1.447 (0.018)
LS mean change from baseline (SE) day 84, L	0.174 (0.015)	0.094 (0.016)	0.142 (0.018)	0.114 (0.018)
LS MD (95% CI)	0.080 (0.037 to 0.124)		0.029 (–0.022 to 0.080)	
P value	*P* < 0.001		*P* = 0.267	
Inspiratory Capacity, Pre-dose				
LS mean baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change at week 12 (SE), L	[redacted]	[redacted]	[redacted]	[redacted]
LS MD (95% CI)	[redacted]		[redacted]	
P value	[redacted]	[redacted]	[redacted]	
SGRQ Total Score				
Week 12	[redacted]	[redacted]	[redacted]	[redacted]
LS MD (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]
Symptoms				
Mean (SD) baseline	NR	NR	NR	NR
Mean (SD) weeks 1 to 52	NR	NR	NR	NR
P value	NR	NR	NR	NR
Deaths (All-Cause)				

	Study 3109		Study 2352	
	FF/V 100/25 N = 260	FP/S 250/50 N = 259	FF/V 100/25 N = 259	FP/S 250/50 N = 252
On treatment, n (%)	0	1	1	0
During follow-up, n (%)				
Deaths, COPD				
On treatment, n (%)	0	0	0	0
Moderate/Severe Exacerbations				
Total	NR	NR	NR	NR

CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FF/V = fluticasone furoate + vilanterol; FP/S = fluticasone propionate + salmeterol; LS = least squares; MD = mean difference; NR = not reported; SD = standard deviation; SE = standard error; SGRQ = St. George's Respiratory Questionnaire
Source: Clinical Study Reports for study 3109, [12] and study 2352.[13]

TABLE 27: KEY EFFICACY OUTCOMES ACTIVE-CONTROLLED (TIOTROPIUM)

	Study 5805	
	FF/V 100/25 N = 310	TIO 18 N = 313
FEV_1, 0- to 24-Hours Weighted Mean		
LS mean at day 84 (L)	[redacted]	[redacted]
LS mean change from baseline (SE) day 84, L	[redacted]	[redacted]
LS MD (95% CI)	[redacted]	
P value	[redacted]	
Trough FEV_1		
LS mean (SE) baseline	[redacted]	[redacted]
LS mean (SE) day 85, L	[redacted]	[redacted]
LS MD (95% CI)	[redacted]	
P value	[redacted]	
Inspiratory Capacity, Pre-Dose		
LS mean baseline (SE)	[redacted]	[redacted]
LS mean change at week 12 (SE), L	[redacted]	[redacted]
LS MD (95% CI)	[redacted]	
P value	[redacted]	
SGRQ Total Score		
Week 12, mean (SD) change	[redacted]	[redacted]
LS MD (95% CI)	[redacted]	
P value	[redacted]	
Symptoms (Cough)		
Mean (SD) change from baseline, weeks 1 to 12	[redacted]	[redacted]
Between-group difference of change from baseline (95% CI)	[redacted]	
P value	[redacted]	
Symptoms (Breathless)		
Mean (SD) change from baseline, weeks 1 to 12	[redacted]	[redacted]
Between-group difference of change from baseline (95% CI)	[redacted]	

	Study 5805	
	FF/V 100/25 N = 310	**TIO 18 N = 313**
P value	[redacted]	
Symptoms (Sputum)		
Mean (SD) change from baseline, weeks 1 to 12	[redacted]	[redacted]
Between-group difference of change from baseline (95% CI)	[redacted]	
P value	[redacted]	
Deaths (All-Cause)		
On treatment, n (%)	0	2
During follow-up, n (%)		
Deaths, COPD		
On treatment, n (%)	0	0
Exacerbations		
Total	[redacted]	[redacted]
Resolved	[redacted]	[redacted]
Resolved with oral CS	[redacted]	[redacted]
Hospitalized	[redacted]	[redacted]
Treated with antibiotics	[redacted]	[redacted]
Withdrawn due to exacerbation	[redacted]	[redacted]

CI = confidence interval; COPD = chronic obstructive pulmonary disease; CS = corticosteroids; FEV_1 = forced expiratory volume in 1 second; FF/V = fluticasone furoate + vilanterol; LS = least squares; MD = mean difference; NR = not reported; SD = standard deviation; SE = standard error; SGRQ = St. George's Respiratory Questionnaire; TIO = tiotropium.
Source: Clinical Study Report for study 5805,[14] Health Canada Review.[33]

TABLE 28: KEY EFFICACY OUTCOMES: PLACEBO-CONTROLLED

	Study 2206				Study 2207			
FEV_1, 0- to 4-Hour Weighted Mean	FF/V 100/25 N = 206	Placebo N = 207	FF 100 N = 206	V25 N = 205	FF/V 100/25 N = 204	Placebo N = 205	FF 100 N = 204	V25 N = 203
Mean (SD) day 168	[redacted]							
Mean (SD) change from baseline, day 168	[redacted]							
Between-group difference (vs. placebo) (95% CI)	[redacted]							
P value (vs. placebo)	[redacted]							
Trough FEV_1								
Mean (SD) day 169	[redacted]							
Mean (SD) change from baseline, day 169	[redacted]							
Between-group difference (vs. placebo) (95% CI)	[redacted]							
P value (vs. placebo)	[redacted]							
CRQ-SAS (Dyspnea)								
Mean (SD) change from baseline, day 168	[redacted]							
Between-group difference (vs. placebo) (95% CI)	[redacted]							
P value (vs. placebo)	[redacted]							
CRQ-SAS (Total)								
Mean (SD) change from baseline, day 168	[redacted]							
Between-group difference (vs. placebo) (95% CI)	[redacted]							
P value (vs. placebo)	[redacted]							

	Study 2206				Study 2207			
FEV_1, 0- to 4-Hour Weighted Mean	FF/V 100/25 N = 206	Placebo N = 207	FF 100 N = 206	V25 N = 205	FF/V 100/25 N = 204	Placebo N = 205	FF 100 N = 204	V25 N = 203
Symptoms (Cough)								
LS mean (SE), weeks 1–24	[redacted]							
Between-group difference (vs. placebo) (95% CI)	[redacted]				[redacted]			
P value (vs. placebo)	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Symptoms (Sputum)								
LS mean (SE), weeks 1 to 24	[redacted]							
Between-group difference (vs. placebo) (95% CI)	[redacted]				[redacted]			
P value (vs. placebo)	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Symptoms (Breathless)								
LS mean (SE), weeks 1 to 24	[redacted]							
Between-group difference (vs. placebo) (95% CI)	[redacted]				[redacted]			
P value (vs. placebo)	[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Deaths								
On treatment, n (%)	[redacted]							
During follow-up, n (%)	[redacted]							
Exacerbations								
Patients, n (%)	[redacted]							

CI = confidence interval; COPD = chronic obstructive pulmonary disease; CRQ-SAS = Chronic Respiratory Questionnaire Self-Administered Standardized; CS = corticosteroids; FEV_1 = forced expiratory volume in 1 second; FF = fluticasone furoate; FF/V = fluticasone furoate + vilanterol; LS = least squares; NR = not reported; SD = standard deviation; SE = standard error; SGRQ = St. George's Respiratory Questionnaire; TIO = tiotropium; V = vilanterol.
Source: Clinical Study Reports for studies 2206[15] and 2207, [16] and Health Canada Review.[33]

TABLE 29: KEY EFFICACY OUTCOMES: VILANTEROL-CONTROLLED

	Study 2871		Study 2970	
	FF/V 100/25 N = 403	V25 N = 409	FF/V 100/25 N = 403	V25 N = 409
Trough FEV_1				
LS mean (SE) week 52	1.238 (0.0112)	1.180 (0.0114)	1.242 (0.0115)	1.219 (0.0116)
LS mean (SE) change from baseline, week 52	0.018 (0.0112)	–0.040 (0.0114)	0.005 (0.0115)	–0.019 (0.0116)
Between-group difference of change from baseline (95% CI)	0.058 (0.027, 0.090)			
P value	*P* < 0.001		*P* = 0.143	
Dyspnea Scores (IVRS Diary)				
LS mean (SE), weeks 1 to 52	–0.31 (0.02) N = 399	–0.23 (0.02) N = 407	–0.20 (0.02) N = 401	–0.09 (0.02) N = 407
Between-group difference (95% CI)	–0.08 (–0.14 to –0.01)		–0.11 (–0.17, –0.05)	
P value	*P* = 0.019		*P* < 0.001	
Symptoms (Percentage 24-Hour Periods With Increased Sputum)				
Mean (SD) baseline	10.1 (22.8)	7.7 (18.5)	9.2 (18.1)	8.9 (19.8)
Mean (SD) weeks 1 to 52	7.7 (14.4) N = 402	7.7 (13.1) N = 408	8.6 (13.8) N = 401	9.7 (16.0) N = 408
P value				
Deaths (All-Cause)				
On treatment, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
During follow-up, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Deaths, COPD				
On treatment, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Moderate/Severe Exacerbations				
Annual rate, LS mean	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	
All Exacerbations				
Annual rate, LS mean	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]	
Time to First Moderate or Severe Exacerbation				
Hazard ratio (95% CI)	0.72 (0.59 to 0.89)		0.80 (0.66 to 0.99)	
	P = 0.002		*P* = 0.036	
Moderate Exacerbations				
Total	[redacted]	[redacted]	[redacted]	[redacted]
Number of home visits	[redacted]	[redacted]	[redacted]	[redacted]
Number of physician visits	[redacted]	[redacted]	[redacted]	[redacted]
Number of urgent/outpatient visits	[redacted]	[redacted]	[redacted]	[redacted]
Number of emergency department	[redacted]	[redacted]	[redacted]	[redacted]

	Study 2871		Study 2970	
	FF/V 100/25 N = 403	V25 N = 409	FF/V 100/25 N = 403	V25 N = 409
visits				
Number of in-patient hospital days (ICU)	[redacted]	[redacted]	[redacted]	[redacted]
Number of in-patient hospital days (ward)	[redacted]	[redacted]	[redacted]	[redacted]
Severe Exacerbations				
Total	[redacted]	[redacted]	[redacted]	[redacted]
Number of home visits	[redacted]	[redacted]	[redacted]	[redacted]
Number of physician visits	[redacted]	[redacted]	[redacted]	[redacted]
Number of urgent/outpatient visits	[redacted]	[redacted]	[redacted]	[redacted]
Number of emergency department visits	[redacted]	[redacted]	[redacted]	[redacted]
Number of in-patient hospital days (ICU)	[redacted]	[redacted]	[redacted]	[redacted]
Number of in-patient hospital days (ward)	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FF/V = fluticasone furoate + vilanterol; ICU = intensive care unit; IVRS = interactive voice response system; LS = least squares; SD = standard deviation; SE = standard error; V = vilanterol.
Source: Clinical Study Reports for study 2871[17] and study 2970,[18] Health Canada Review.[33]

TABLE 30: KEY EFFICACY OUTCOMES: CROSSOVER TRIAL

	Study 946	
FEV_1, 0- to 24-Hours Weighted Mean	**FF/V 100/25 N = 33**	**Placebo N = 51**
LS mean (SE) baseline	1.517 (0.0282)	1.297 (0.0240)
LS mean (SE) change from baseline, day 29	0.164 (0.0282)	–0.056 (0.0240)
Between-group difference of change from baseline (95% CI)	0.220 (0.165 to 0.275) < 0.001	
P value	*P* < 0.001	
Trough FEV_1		
LS mean (SE) day 29	1.506 (0.035)	1.328 (0.029)
LS mean (SE) change from baseline, day 29	0.153 (0.035)	–0.024 (0.029)
Between-group difference of change from baseline (95% CI)	0.177 (0.097 to 0.257)	
P value	*P* < 0.001	
Dyspnea Scores	NR	NR
Symptoms (Percentage 24-Hour Periods With Increased Sputum)	NR	NR
Deaths (All-Cause)		
On treatment, n (%)	0	0
During follow-up, n (%)	0	0
Deaths, COPD		
On treatment, n (%)	0	0

	Study 946	
FEV_1, 0- to 24-Hours Weighted Mean	FF/V 100/25 N = 33	Placebo N = 51
Moderate or Severe Exacerbation	NR	NR

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second; FF/V = fluticasone furoate + vilanterol; LS = least squares; NR = not reported; SE = standard error; V = vilanterol.
Source: Clinical Study Report for study 946.[19]

3.7 Harms

Only those harms identified in the review protocol (see Table 5) are presented here. The harms data are presented in Table 31 through Table 34. For detailed harms data, see APPENDIX 5: DETAILED OUTCOME DATA.

3.7.1 Adverse Events

The proportion of patients with an adverse event (AE) differed across the active-controlled studies, ranging between 20% and 36%. There were a larger proportion of patients with an AE in the 24-week placebo-controlled trials (range 38% to 60% across groups), with differences, but no consistent differences between groups across the studies. For example, in study 2206, the fluticasone furoate monotherapy group had the highest proportion of patients with AEs (60%), while in study 2207 the fluticasone furoate group had the lowest proportion of patients with an AE (38%). Headache was the most common AE across groups and studies. The proportion of patients with an AE was even higher in the 52-week vilanterol-controlled studies, with an incidence of 77% with fluticasone furoate plus vilanterol and 71% with vilanterol.

3.7.2 Serious Adverse Events

SAEs were infrequent, ranging between 1% and 5% across the 12-week active-controlled studies. In the placebo-controlled studies, the proportion of patients with an SAE was higher, ranging between 3% and 8%. And in the 52-week vilanterol-controlled studies, the proportion of patients with SAEs ranged between 14% and 17%. COPD was the most common event.

3.7.3 Withdrawal Due to Adverse Events

Withdrawals due to adverse events ranged between less than 1% and 4% in the 12-week active-controlled studies, 6% and 12% in the placebo-controlled studies, and 5% to 9% in the vilanterol-controlled studies.

3.7.4 Notable Harms

Pneumonia was an infrequent AE (less than 1% of patients), and there was no clear difference in incidence of pneumonia between groups in any of the active-controlled studies. The proportion of patients with pneumonia was also low in the placebo-controlled studies, with too few events to draw any conclusions. Across the two placebo-controlled studies, there were six fluticasone furoate plus vilanterol patients with pneumonia and three placebo patients.

In the 52-week vilanterol-controlled studies, the proportion of patients with pneumonia was higher than in the other studies, with 51 of fluticasone furoate plus vilanterol patients (6%) with pneumonia versus 27 vilanterol patients (3%). There was one pneumonia-related death with fluticasone furoate plus vilanterol in study 2970.

TABLE 31: HARMS: ACTIVE (FLUTICASONE PROPIONATE PLUS SALMETEROL)-CONTROLLED

	Study 3107		Study 6974		Study 3109		Study 2352	
AEs	**FF/V 100/25 N = 266**	**FP/S 500/50 N = 262**	**FF/V 100/25 N = 412**	**FP/S 250/50 N = 416**	**FF/V 100/25 N = 260**	**FP/S 250/50 N = 259**	**FF/V 100/25 N = 259**	**FP/S 250/50 N = 252**
Patients with > 0 AEs, n (%)	73 (27)	68 (26)	132 (32)	136 (33)	69 (25)	66 (25)	53 (20)	59 (23)
Most common AEs[a]								
Nasopharyngitis	8 (3)	12 (5)	30 (7)	26 (6)	8 (3)	7 (3)	6 (2)	5 (2)
Oral candidiasis	2 (< 1)	4 (2)	5 (1)	7 (2)	1 (< 1)	5 (2)	2 (< 1)	7 (3)
Oropharyngeal candidiasis	0	3 (1)	3 (< 1)	2 (< 1)	0	2 (< 1)	4 (2)	7 (3)
Headache	20 (8)	18 (7)	18 (4)	29 (7)	16 (6)	11 (4)	12 (5)	10 (4)
Pneumonia	1 (< 1)	2 (< 1)	2 (< 1)	4 (< 1)	1 (< 1)	0	2 (< 1)	0
SAEs								
Patients with > 0 SAEs, n (%)	6 (2)	3 (1)	13 (3)	20 (5)	3 (1)	8 (3)	5 (2)	3 (1)
Most common SAEs								
COPD	1 (< 1)	0	5 (1)	4 (< 1)	0	3 (1)	1 (< 1)	0
Pneumonia	1 (< 1)	2 (< 1)	1 (< 1)	4 (< 1)	0	0	0	0
WDAEs								
WDAEs, n (%)	6 (2)	3 (1)	14 (3)	16 (4)	4 (2)	8 (3)	5 (2)	1 (< 1)
Deaths								
Most common reasons	CHF		GI hemorrhage	Cardiac failure (2)	0	Cardio-respiratory arrest	Cardiac failure, respiratory failure, MI	
				Lung cancer				

AE = adverse event; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CRQ-SAS = Chronic Respiratory Questionnaire Self-Administered Standardized; FF/V = fluticasone furoate + vilanterol; FP/S = fluticasone propionate plus salmeterol; GI = gastrointestinal; MI = myocardial infarction; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Source: Clinical Study Reports for study 3107,[10] study 6974,[11] study 3109,[12] and study 2352.[13]

TABLE 32: HARMS — TIOTROPIUM-CONTROLLED

	Study 5805	
AEs	**FF/V 100/25 N = 310**	**TIO 18 N = 313**
Patients with > 0 AEs, n (%)	113 (36)	99 (32)
Most common AEs		
Nasopharyngitis	16 (5)	13 (4)
Oral candidiasis	9 (3)	5 (2)
Oropharyngeal candidiasis	2 (< 1)	0
Headache	18 (6)	23 (7)
Pneumonia	2 (< 1)	0
SAEs		
Patients with > 0 SAEs, n (%)	10 (3)	10 (3)
Most common SAEs		
COPD	2 (< 1)	1 (< 1)
Pneumonia	3 (< 1)	0
WDAEs		
WDAEs, n (%)	6 (2)	12 (4)
Most common reasons		
Number of Deaths, n (%)	0	2 (< 1)
Reasons		Cardiorespiratory arrest
		Cardiorespiratory arrest, cardiac failure

AE = adverse event; COPD = chronic obstructive pulmonary disease; FF/V = fluticasone furoate + vilanterol; SAE = serious adverse event; TIO = tiotropium; WDAE = withdrawal due to adverse event.
Source: Clinical Study Report for study 5805.[14]

TABLE 33: HARMS — PLACEBO-CONTROLLED

	Study 2206				Study 2207			
AEs	**FF/V 100/25 N = 206**	**Placebo N = 207**	**FF 100 N = 206**	**V25 N = 205**	**FF/V 100/25 N = 204**	**Placebo N = 205**	**FF 100 N = 204**	**V25 N = 203**
Patients with > 0 AEs, n (%)	111 (54)	100 (48)	123 (60)	111 (54)	92 (45)	96 (47)	78 (38)	85 (42)
Most common AEs								
Nasopharyngitis	22 (11)	14 (7)	18 (9)	22 (11)	13 (6)	17 (8)	14 (7)	19 (9)
URTI	21 (10)	8 (4)	13 (6)	11 (5)	8 (4)	5 (2)	3 (1)	9 (4)
Oral candidiasis	4 (2)	1 (< 1)	2 (< 1)	3 (1)	8 (4)	2 (< 1)	5 (2)	2 (< 1)
Oropharyngeal candidiasis	6 (3)	2 (< 1)	4 (2)	2 (< 1)	3 (1)	3 (1)	0	1 (< 1)
Headache	18 (9)	5 (2)	17 (8)	16 (8)	11 (5)	15 (7)	13 (6)	20 (10)
SAEs								
Patients with > 0 SAEs, n (%)	11 (5)	11 (5)	16 (8)	15 (7)	12 (6)	10 (5)	6 (3)	16 (8)
Most common SAEs								
COPD	4 (2)	3 (1)	2 (< 1)	6 (3)	5 (2)	5 (2)	0	5 (2)
Pneumonia	1 (< 1)	1 (< 1)	2 (< 1)	3 (1)	0	0	0	2 (< 1)
WDAEs								
WDAEs, n (%)	14 (7)	15 (7)	23 (11)	24 (12)	17 (8)	18 (9)	12 (6)	15 (7)
Deaths								
Reason		Sudden death (post-treatment)	PE (post-treatment)	Sudden cardiac	Stroke	Heart disease		Anaphylaxis
Reason					Unknown (post-treatment)			Poisoning
Notable Harms, n (%)								
AE (pneumonia)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; COPD = chronic obstructive pulmonary disease; CRQ-SAS = Chronic Respiratory Questionnaire Self-Administered Standardized; FF = fluticasone furoate; FF/V = fluticasone furoate + vilanterol; PE = pulmonary embolism; SAE = serious adverse event; URTI = upper respiratory tract infection; V = vilanterol; WDAE = withdrawal due to adverse event.
Source: Clinical Study Reports for studies 2206[15] and 2207.[16]

TABLE 34: HARMS — VILANTEROL-CONTROLLED/CROSSOVER

	Study 2871		Study 2970		Study 946	
Adverse Events	**FF/V 100/25 N = 403**	**V25 N = 409**	**FF/V 100/25 N = 403**	**V25 N = 409**	**FF/V 100/25 N = 33**	**Placebo N = 51**
Patients with > 0 AEs, n (%)	301 (75)	281 (69)	320 (79)	294 (72)	4 (12)	2 (4)
Most common AEs						
Nasopharyngitis	60 (15)	54 (13)	68 (17)	58 (14)	0	0
URTI	51 (13)	47 (11)	39 (10)	31 (8)	1 (3)	0
Oral candidiasis	34 (8)	21 (5)	39 (10)	29 (7)	0	0
Oropharyngeal candidiasis	7 (2)	2 (< 1)	11 (3)	3 (< 1)	0	0
Headache	25 (6)	30 (7)	32 (8)	30 (7)	0	0
Pneumonia	25 (6)	16 (4)	26 (6)	11 (3)	0	0
SAEs						
Patients with > 0 SAEs, n (%)	56 (14)	60 (15)	67 (17)	66 (16)	0	0
Most common SAEs						
COPD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WDAEs						
WDAEs, n (%)	29 (7)	22 (5)	35 (9)	25 (6)	0	0
Most common reasons						
Deaths						
Most common reasons	[redacted]	[redacted]	[redacted]	[redacted]		
	[redacted]	[redacted]	[redacted]	[redacted]		
	[redacted]	[redacted]	[redacted]	[redacted]		
	[redacted]	[redacted]				
	[redacted]					

ACS = acute coronary syndrome; AE = adverse event; ARF = acute respiratory failure; COPD = chronic obstructive pulmonary disease; CRA = cardiorespiratory arrest; FF = fluticasone furoate; FF/V = fluticasone furoate + vilanterol; MI = myocardial infarction; SAE = serious adverse event; URTI = upper respiratory tract infection; V = vilanterol; WDAE = withdrawal due to adverse event.
Source: Clinical Study Report for study 946, [19] study 2871[17] and study 2970.[18]

4. DISCUSSION

4.1 Summary of Available Evidence

Ten DB RCTs were included in this review. Of the five active-controlled studies, four compared fluticasone furoate plus vilanterol with fluticasone propionate plus salmeterol, and one compared fluticasone furoate plus vilanterol with tiotropium, all over a treatment period of 12 weeks. Two studies compared fluticasone furoate plus vilanterol and its various components to placebo, over 24 weeks, and two studies compared fluticasone furoate plus vilanterol to vilanterol over 52 weeks of therapy. Finally, a crossover study with a placebo control was also included. There were no consistent differences between fluticasone furoate plus vilanterol and fluticasone propionate plus salmeterol, or tiotropium for the FEV_1 primary outcomes tested, and fluticasone furoate plus vilanterol was superior to placebo for the primary outcomes related to FEV_1. Additionally, in the 52-week studies, fluticasone furoate plus vilanterol was superior to vilanterol for annualized exacerbation rate. The proportion of patients with AEs increased with increasing treatment periods, although there were no clear trends with respect to differences between groups. AEs of interest included pneumonia, and although there were no clear differences in incidence of pneumonia between groups in the 12-week active-controlled studies or in the 24-week placebo-controlled studies, there appeared to be a higher incidence of pneumonia with fluticasone furoate plus vilanterol versus vilanterol in the 52-week studies.

Key critical appraisal issues include the short duration of the 12-week active-comparator studies versus fluticasone propionate plus salmeterol and tiotropium, particularly for assessing important harms such as pneumonia. External validity issues include the relatively young population (minimum age of 40) and the high proportion of patients exhibiting bronchodilator reversibility, suggestive of asthma.

4.2 Interpretation of Results

4.2.1 Efficacy

Of the 10 included studies, the five 12-week studies all had an active control (fluticasone propionate plus salmeterol or tiotropium), while the longest-duration studies (52 weeks) were those that had vilanterol as a control. A key comparator for fluticasone furoate plus vilanterol is another ICS/LABA combination; therefore, it is not clear why the studies that featured that ICS/LABA combination were of the shortest duration, while the longest-duration studies were those that assessed fluticasone furoate plus vilanterol versus a component of fluticasone furoate plus vilanterol. From an ethical standpoint, a study that featured a ICS/LABA control would be just as likely to address any concerns over maintaining patient care as a study that featured LABA monotherapy, where the LABA monotherapy was also a new drug.

Mortality in general and mortality due to COPD were key efficacy outcomes of this review; however, none of the included studies were adequately powered or of sufficient duration to assess this outcome. This was particularly the case for the 12-week active-controlled studies, which were of sufficient duration only to assess pulmonary function. Exacerbations were another key efficacy outcome that were not rigorously assessed in the included studies. Annualized exacerbation rates were a primary outcome of two studies; however, both of those studies were vilanterol-controlled. The lack of a study designed to examine differences in exacerbation rates between fluticasone furoate plus vilanterol and another ICS/LABA comparator is a major limitation of this review. Exacerbations are a key cost driver and, according to the patient-impact statement submitted to CDR, exacerbations are of major concern to patients. Exacerbations can lead to hospitalizations, which put these patients, many of whom are elderly, at risk of acquiring nosocomial infections such as pneumonia when they are already at higher

risk of contracting and experiencing morbidity and death from pneumonia. Exacerbations may also lead to use of systemic corticosteroids, accompanied by a long list of very serious adverse effects. Thus, exacerbations are a critical part of COPD, yet these 10 included studies provide limited insight into the impact of fluticasone furoate plus vilanterol on this key outcome.

Quality of life is also an important consideration in COPD, and this was supported by feedback provided by patients in their impact statement to CDR. Quality of life was assessed in only one of the four studies (with fluticasone propionate plus salmeterol, [redacted]) and there was no statistically significant difference in SGRQ total score between fluticasone furoate plus vilanterol and fluticasone propionate plus salmeterol. The fact that there was no difference in quality of life between active therapies is not surprising, particularly with ICS/LABA combinations, as the drugs have similar efficacy and side-effect profiles. Although in the placebo-controlled studies fluticasone furoate plus vilanterol did statistically improve CRQ-SAS dyspnea and total scores versus placebo, only about 75% of the population was sampled, and the difference between fluticasone furoate plus vilanterol and placebo did not meet the MCID of 0.5 for a single item. Therefore, the quality of evidence on fluticasone furoate plus vilanterol is limited.

The once-daily dosing afforded by fluticasone furoate plus vilanterol, as well as the new 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, compliance was high in all included studies, and was at least 97% in all of the trials that compared fluticasone furoate plus vilanterol to fluticasone propionate plus salmeterol, and there was no difference in compliance between groups. Compliance is typically high in clinical trials, where patients are closely monitored and are usually a motivated population that is more likely to follow instruction. Therefore, with the high compliance rates in both groups, there is no way of knowing whether this new inhaler design will indeed lead to better compliance. It is widely accepted that patients prefer a once-daily frequency of administration and that the more frequent the administration, the more likely adherence will suffer. Although there is some evidence (see Appendix 7 for details) of patient preference for the Ellipta over other devices, the impact of this preference on patient adherence will likely need to be addressed in the post-marketing setting with an effectiveness study.

Across the studies, approximately 30% of patients demonstrated reversibility to salbutamol at baseline, and this is higher than one would expect to see in a COPD population. Baseline reversibility to salbutamol may indicate that a given patient has asthma in addition to their COPD, and this enhanced responsiveness to salbutamol may indicate that they are more likely to have positive FEV_1 responses if they received vilanterol, a LABA, either as monotherapy or as fluticasone furoate plus vilanterol, on study. Indeed, in the studies that compared fluticasone furoate plus vilanterol to vilanterol, the FEV_1 data were mixed, with a statistically significant improvement with fluticasone furoate plus vilanterol over vilanterol in one study, but not in the other. Subgroup data were available for baseline reversibility status for a number of studies. In the studies that compared fluticasone furoate plus vilanterol to fluticasone propionate plus salmeterol, there was no clear pattern in FEV_1 0 to 24 hours responses based on baseline reversibility status. For example, patients demonstrating non-reversibility appeared to have better responses to fluticasone furoate plus vilanterol than fluticasone propionate plus salmeterol in study 3109, but not in the other studies. Conversely, patients with reversibility at baseline had better responses with fluticasone furoate plus vilanterol than fluticasone propionate plus salmeterol in study 3107. In the placebo-controlled study 2206, both patients demonstrating reversibility and those demonstrating non-reversibility had statistically larger improvement in trough FEV_1 with fluticasone furoate plus vilanterol versus placebo. [redacted]

[redacted] According to the clinical expert, measurements of IC might provide a measure of pulmonary function that is more specific to COPD, and this would have been one way to determine whether fluticasone furoate plus vilanterol is having a positive effect on COPD, rather than treating underlying asthma. [redacted] IC responses were not assessed in the placebo- or vilanterol-controlled studies.

There were no studies that directly compared fluticasone furoate plus vilanterol versus budesonide plus formoterol. A published network meta-analysis by Oba in May 2014 reviewed all the various ICS/LABA combinations in patients with severe COPD, focusing on their efficacy with respect to moderate and severe exacerbations.[43] The analysis included 21 studies for moderate to severe exacerbations (N = 26,868 patients) and 13 studies (19,368 patients) for severe exacerbations. All studies were DB RCTs. Among the five ICS/LABA combinations studied, there were 3,878 patients treated with fluticasone furoate plus vilanterol, 7,667 patients treated with budesonide plus formoterol, and 12,354 patients treated with fluticasone propionate plus salmeterol in the analysis. All of these combinations reduced moderate to severe exacerbations. None of the ICS/LABA combinations reduced severe exacerbations when compared with placebo or LABA. A key limitation of the Oba analysis was that it failed to include any of the five active-comparator trials that included fluticasone furoate plus vilanterol. All of these studies were included in the CDR review. Additionally, no spirometry data were reported and, importantly, no pneumonia data were reported. A recent poster by Stynes included one of the trials that directly compared fluticasone furoate plus vilanterol with fluticasone propionate plus salmeterol in their network meta-analysis; however, this analysis was manufacturer-sponsored and it is only available in the form of a poster, which limits the critical appraisal that can be performed.[44] The poster found a lack of sufficient data to draw conclusions on exacerbations, but did find comparable efficacy of fluticasone furoate plus vilanterol, with both fluticasone propionate plus salmeterol and budesonide plus formoterol for FEV_1 and for quality of life by the SGRQ.

4.2.2 Harms

COPD patients treated with ICS are at higher risk of pneumonia [42] and at higher risk of morbidity and mortality from pneumonia; thus, pneumonia is a notable harm when assessing any ICS/LABA combination for COPD. Not surprisingly, as the duration of treatment lengthened from 12 to 24 to 52 weeks, the proportion of patients experiencing pneumonia also increased. It is only in the 52-week studies that there are enough patients with pneumonia to begin to see whether there is an increased incidence with fluticasone furoate plus vilanterol over its comparator, and in these studies there were seven pneumonia-related deaths with the higher fluticasone furoate plus vilanterol 200/25 mcg dose, prompting additional concern over whether the longer-acting ICS, fluticasone furoate, might carry additional risk of pneumonia compared with other ICS. However, there was only one death in the approved fluticasone furoate plus vilanterol 100/25 mcg dose, suggesting that the increased risk of pneumonia is dose-related. However, the problem with this study is that the only comparator is vilanterol, rather than another ICS/LABA combination and/or placebo. As noted above, in the placebo-controlled studies, six fluticasone furoate plus vilanterol patients and three placebo patients had

pneumonia. Given that the use of ICS in COPD is associated with increased risk of pneumonia, these findings merely generate the hypothesis that fluticasone furoate plus vilanterol might carry an increased risk of pneumonia, as do other ICS/LABA combinations. Unfortunately, the most important and potentially informative comparison for assessing risk of pneumonia with fluticasone furoate plus vilanterol would be the comparative studies versus fluticasone propionate plus salmeterol and tiotropium, and these studies were of too short a duration to draw any conclusions about risk of pneumonia relative to relevant comparators.

4.3 Other Considerations

- According to the Health Canada review, fluticasone furoate plus vilanterol is the first drug to be approved in Canada for the reduction of COPD exacerbations.

[redacted]

- Neither fluticasone furoate nor vilanterol are approved as separate inhalers in Canada.

5. CONCLUSIONS

Results from five active-comparator trials suggest similar efficacy with respect to improvements in FEV_1 and frequency of exacerbations for fluticasone furoate plus vilanterol versus fluticasone propionate plus salmeterol, and similar efficacy for FEV_1 versus tiotropium, over the course of 12 weeks. The study that compared fluticasone furoate plus vilanterol versus tiotropium did not report exacerbations as an efficacy outcome. Fluticasone furoate plus vilanterol reduced exacerbations over one year versus vilanterol alone, although there were inconsistent results for improvements in FEV_1 when fluticasone furoate plus vilanterol was compared with vilanterol monotherapy. Harms, including pneumonia, were similar between fluticasone furoate plus vilanterol and either fluticasone propionate plus salmeterol or tiotropium. In the 52-week studies, the incidence of pneumonia was numerically higher with fluticasone furoate plus vilanterol than with vilanterol monotherapy. Studies with longer duration of treatment would be needed to determine whether there are differences in the risk of pneumonia between fluticasone furoate plus vilanterol and other active comparators.

APPENDIX 2: PATIENT INPUT SUMMARY

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

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

The New Brunswick Lung Association (NBLA) is a provincial member of the Canadian Lung Association, which has more than 100 years of experience in the delivery of community health programs and in support for and coordination of respiratory health research. NBLA also delivers its services in Nunavut. The NBLA is the national lead on environmental issues for the Canadian Lung Association. With respect to activities related to the Federal Tobacco Control Strategy, the NBLA was instrumental in achieving the province's *Smoke-Free Places Act* and has successfully achieved legislation to prevent smoking in vehicles with children under 19 years old. The NBLA has delivered smoking-cessation programs in First Nations communities and workplaces. It is currently working on the development of improved policies for tobacco reduction in lower socio-economic groups. The NBLA is a partner in the national initiative that will be implementing the National Lung Health Framework for Canada. As well, the Association developed a Provincial Framework for Asthma and COPD.

NBLA receives funding for a health symposium and patient counselling from Takeda, AstraZeneca, Boehringer Ingelheim, Merck, Pfizer, GlaxoSmithKline, and Actelion. NBLA declared no conflicts of interest in the preparation of this submission.

2. Condition and Current Therapy-Related Information

Information was gathered directly from patients speaking to the NBLA's registered nurse and from the NBLA's BreathWorks helpline.

Over time, patients with COPD have increasing debility. Those with moderate to severe COPD have difficulty performing daily tasks such as dressing or walking. Their symptoms worsen with exposure to air pollutants and humidity and when they have respiratory infections. Those who have experienced exacerbations have a permanently worsened condition. The prevention of exacerbations is a key goal for COPD patients.

Patients receive benefits from a variety of current therapies, including prescription drugs and exercise programs; however, given the rate of hospitalization for COPD in New Brunswick, these treatments are not sufficient to control exacerbations. Each exacerbation results in a decrease in lung function for patients.

Patients with moderate to severe COPD require home help. While current treatments slow the decline of lung function, they do not prevent exacerbations. Thus, patients need increasing support either from a family member, paid nurse, or the New Brunswick Extra-Mural Program. Oxygen therapy is often difficult to afford in New Brunswick as oxygen is not covered by health insurance plans.

3. Related Information About the Drug Being Reviewed

The NBLA did not describe any patient experience with fluticasone furoate/vilanterol in this submission. NBLA notes that this drug reduces COPD exacerbations. Because exacerbations create sudden and permanent reductions in lung function, preventing exacerbations should be a key goal for COPD patients, given that COPD cannot be cured. There is a need for a new drug to effectively prevent COPD exacerbations and to slow down the decline in lung function so that patients can remain relatively self-sufficient for as long as possible.

APPENDIX 3: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase Ovid MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of search:	March 20, 2014
Alerts:	Monthly search updates began March 20, 2014 and ran until July 16, 2014.
Study types:	All.
Limits	No limits used.

Syntax Guide	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number

MULTI-DATABASE STRATEGY		
1	(breoellipta* or breo ellipta* or relvar ellipta* or relvarellipta*).ti, ab, hw, ot, rn, nm.	4
2	fluticasone*.ti, ab, hw, ot, rn, nm.	15772
3	vilanterol*.ti, ab, hw, ot, rn, nm.	217
4	2 and 3	140
5	1 or 4	140
6	remove duplicates from 5	107

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Cochrane Library March 2014	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.

Grey Literature

Dates for Search:	March 2014
Keywords:	Breo Ellipta, (vilanterol and fluticasone)
Limits:	None

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

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Databases (free)
- Internet Search.

APPENDIX 4: EXCLUDED STUDIES

Reference	Reason for Exclusion
Kempsford R, et al. Pulm Pharmacol Ther. 2013 Apr;26(2):256-64	Not randomized controlled trial
Lotvall J, et al. BMJ Open 2012	Wrong dose

APPENDIX 5: DETAILED OUTCOME DATA

Exposure

TABLE 35: EXPOSURE TO STUDY MEDICATION (FLUTICASONE PROPIONATE PLUS SALMETEROL-CONTROLLED STUDIES)

	Study 3107		Study 3109		Study 2352		Study 6974	
	FF/V 100/25 N = 266	FP/S 500/50 N = 262	FF/V 100/25 N = 260	FP/S 250/50 N = 259	FF/V 100/25 N = 259	FP/S 250/50 N = 252	FF/V 100/25 N = 412	FP/S 250/50 N = 416
Mean (SD) exposure, days	[redacted]							
Concomitant Medications Used During Study								
COPD medications	[redacted]							
Ipratropium	[redacted]							
Salbutamol	[redacted]							
Salmeterol	[redacted]							
FP	[redacted]							
Tiotropium	[redacted]							
Acetylcysteine	[redacted]							
Amoxicillin	[redacted]							
Budesonide	[redacted]							
Oxygen	[redacted]							
Ambroxol	[redacted]							
Non-COPD Medications (by System, Top Three or Four of Interest)								
Cardiovascular	[redacted]							
Nervous	[redacted]							
Alimentary	[redacted]							
Respiratory	[redacted]							

COPD = chronic obstructive pulmonary disease; FF = fluticasone furoate; FF/V = fluticasone furoate + vilanterol; FP = fluticasone propionate; NR = not reported; S = salmeterol; SD = standard deviation.
Source: Clinical Study Reports for study 3107, study 3109, study 2352, study 6974.

TABLE 36: EXPOSURE TO STUDY MEDICATION (TIOTROPIUM-CONTROLLED STUDY)

	Study 5805	
	FF/V 100/25 N = 310	TIO 18 N = 313
Mean (SD) days	[redacted]	
Concomitant medications used during study		
COPD medications	[redacted]	
Ipratropium	[redacted]	
Salbutamol	[redacted]	
Salmeterol	[redacted]	
FP	[redacted]	
Tiotropium	[redacted]	
Acetylcysteine	[redacted]	

	Study 5805	
	FF/V 100/25 N = 310	TIO 18 N = 313
Amoxicillin	[redacted]	[redacted]
Budesonide	[redacted]	[redacted]
Oxygen	[redacted]	[redacted]
Ambroxol	[redacted]	[redacted]
Guaifenesin	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]
Non-COPD medications (by system, top three or four of interest)		
Cardiovascular	[redacted]	[redacted]
Nervous	[redacted]	[redacted]
Alimentary	[redacted]	[redacted]
Respiratory	[redacted]	[redacted]

COPD = chronic obstructive pulmonary disease; FF/V = fluticasone furoate + vilanterol; FP = fluticasone propionate; [redacted] SD = standard deviation; TIO = tiotropium.
Source: Clinical Study Report for study 5805.

TABLE 37: EXPOSURE TO STUDY MEDICATION (PLACEBO-CONTROLLED STUDIES)

	Study 2206				Study 2207			
	FF/V 100/25 N = 206	Placebo N = 207	FF 100 N = 206	V25 N = 205	FF/V 100/25 N = 204	Placebo N = 205	FF 100 N = 204	V25 N = 203
Mean (SD) days	[redacted]							
Medications Used Pre-Treatment								
SABA	[redacted]							
SAAC	[redacted]							
LABA	[redacted]							
LAAC	[redacted]							
ICS	[redacted]							
Xanthine	[redacted]							
Concomitant Medications Used During Study								
Any COPD Medications	[redacted]							
SAAC	[redacted]							
Other respiratory medications	[redacted]							
Antibiotics	[redacted]							
Other COPD medications	[redacted]							
Systemic CS	[redacted]							
SABA	[redacted]							
LABA	[redacted]							

	Study 2206				Study 2207			
	FF/V 100/25 N = 206	Placebo N = 207	FF 100 N = 206	V25 N = 205	FF/V 100/25 N = 204	Placebo N = 205	FF 100 N = 204	V25 N = 203
ICS	[redacted]							
LAAC	[redacted]							
Xanthines	[redacted]							
Other CS	[redacted]							
LTRA	[redacted]							
Non-COPD Medications (by System, Top Three or Four of Interest)								
Cardiovascular	[redacted]							
Nervous	[redacted]							
Alimentary	[redacted]							
Respiratory	[redacted]							

COPD = chronic obstructive pulmonary disease; CS = corticosteroids; FF = fluticasone furoate; FF/V = fluticasone furoate + vilanterol; FP = fluticasone propionate; ICS = Inhaled corticosteroids; LAAC = long-acting anticholinergics; LABA = long-acting beta-agonists; LTRA = leukotriene receptor antagonist; S = salmeterol; SAAC = short-acting anticholinergics; SABA = short-acting beta-agonist; SD = standard deviation; SE = standard error; TIO = tiotropium; V = vilanterol.
Source: Clinical Study Report for studies 2206, 227.

TABLE 38: EXPOSURE TO STUDY MEDICATION (VILANTEROL-CONTROLLED STUDIES)

	Study 2871		Study 2970		Study 946	
	FF/V 100/25 N = 403	V25 N = 409	FF/V 100/25 N = 403	V25 N = 409	FF/V 100/25 N = 33	Placebo N = 51
Mean (SD) days	[redacted]					
COPD Medications						
For moderate exacerbation						
Any medication	[redacted]					
Any antibiotic	[redacted]					
Systemic corticosteroids	[redacted]					
For severe exacerbation						
Any medication	[redacted]					
Systemic corticosteroids	[redacted]					
Non-COPD Medications	[redacted]					
Nervous	[redacted]					
Cardiovascular	[redacted]					
Alimentary	[redacted]					
Respiratory	[redacted]					

COPD = chronic obstructive pulmonary disease; FF/V = fluticasone furoate + vilanterol; SD = standard deviation; V = vilanterol.
Source: Clinical Study Reports for studies 2871, 2970.

Other Efficacy Outcomes

TABLE 39: OTHER EFFICACY OUTCOMES (FLUTICASONE PROPIONATE PLUS SALMETEROL-CONTROLLED STUDIES)

	Study 3107		Study 3109		Study 2352		Study 6974	
Rescue medication use	FF/V 100/25 N = 266	V25 N = 262	FF/V 100/25 N = 260	FP/S 250/50 N = 259	FF/V 100/25 N = 259	FP/S 250/50 N = 252	FF/V 100/25 N = 412	FP/S 250/50 N = 416
LS mean daily use baseline	NR	NR	[redacted]					
LS mean daily use, weeks 1–12	–0.64 (0.08) N = 254	–0.58 (0.08) N = 256	[redacted]					
P value	–0.064 (–0.24, 0.11), *P* = 0.478		[redacted]					
Mean (SD) % of rescue-free 24-hour periods baseline	61.6	58.5	[redacted]					
Mean (SD) % of rescue-free 24-hour periods, weeks 1 to 12	62.5 (38.6) N = 258	59.8 (39.2) N = 258	[redacted]					
P value	NR		[redacted]					
Adherence								
Mean (SD) overall compliance, %	[redacted]		[redacted]		[redacted]		[redacted]	

FF = fluticasone furoate; FF/V = fluticasone furoate + vilanterol; FP/S = fluticasone propionate + salmeterol; LS = least squares; SD = standard deviation; V = vilanterol.

TABLE 40: OTHER EFFICACY OUTCOMES (TIOTROPIUM-CONTROLLED STUDY)

	Study 5805	
Rescue Medication Use	**FF/V 100/25 N = 310**	**TIO 18 N = 313**
LS mean (SD) daily-use baseline	[redacted]	
LS mean daily use, mean change (SD), weeks 1 to 12	[redacted]	
P value	[redacted]	
Mean (SD) % of rescue-free 24-hour periods, baseline	[redacted]	
Mean (SD) % of rescue-free 24-hour periods, weeks 1 to 52	[redacted]	
P value	[redacted]	
Adherence		
Mean (SD) overall compliance, %	[redacted]	

FF = fluticasone furoate; FF/V = fluticasone furoate + vilanterol; LS = least squares; SD = standard deviation; TIO = tiotropium.

TABLE 41: OTHER EFFICACY OUTCOMES (PLACEBO-CONTROLLED STUDIES)

	Study 2206				Study 2207			
Rescue Medication Use	FF/V 100/25 N = 206	Placebo N = 207	FF 100 N = 206	V25 N = 205	FF/V 100/25 N = 204	Placebo N = 205	FF 100 N = 204	V25 N = 203
Mean (SD) daily-use baseline	[redacted]							
Mean (SD) change from baseline, day 168	[redacted]							
Mean (SD) daily use, weeks 1 to 24	[redacted]							
P value	[redacted]							
Mean (SD) % of rescue-free 24-hour periods baseline	[redacted]							
Mean (SD) % of rescue-free 24-hour periods, weeks 1 to 24	[redacted]							
P value	[redacted]							
Adherence								
Mean (SD) overall compliance, %	[redacted]							
Days of missed work/school	[redacted]							

FF = fluticasone furoate; FF/V = fluticasone furoate + vilanterol; NR = not reported; SD = standard deviation; TIO = tiotropium; V = vilanterol.

TABLE 42: OTHER EFFICACY OUTCOMES (VILANTEROL-CONTROLLED STUDIES)

	Study 2871		Study 2970		Study 946	
Rescue Medication Use	FF/V 100/25 N = 403	V25 N = 409	FF/V 100/25 N = 403	V25 N = 409	FF/V 100/25 N = 33	V25 N = 51
LS mean daily use, weeks 1 to 52	[redacted]					
P value	[redacted]					
Mean (SD) % of rescue-free 24-hour periods baseline	[redacted]					
Mean (SD) % of rescue-free 24-hour periods, weeks 1–52	[redacted]					
P value						

	Study 2871		Study 2970		Study 946	
Rescue Medication Use	**FF/V 100/25 N = 403**	**V25 N = 409**	**FF/V 100/25 N = 403**	**V25 N = 409**	**FF/V 100/25 N = 33**	**V25 N = 51**
Adherence						
Mean (SD) overall compliance, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Days of missed work/school	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

FF/V = fluticasone furoate + vilanterol; LS = least squares; SD = standard deviation; V = vilanterol.

Detailed Exacerbation Data

TABLE 43: DETAILED EXACERBATION DATA (PLACEBO-CONTROLLED STUDIES)

	Study 2206				Study 2207			
	FF/V 100/25 N = 206	**Placebo N = 207**	**FF 100 N = 206**	**V25 N = 205**	**FF/V 100/25 N = 204**	**Placebo N = 205**	**FF 100 N = 204**	**V25 N = 203**
Moderate Exacerbations								
Total	15	18	25	15	8	15	4	11
Number of home visits	0	0	0	0	0	2	0	0
Number of physician visits	11	16	16	17	6	26	5	14
Number of urgent/ outpatient visits	5	0	3	0	2	0	0	0
Number of ED visits	2	1	0	1	0	0	0	1
Number of in-patient hospital days (ICU)	NR	NR	NR	NR	0	0	0	0
Number of in-patient hospital days (ward)	NR	NR	NR	NR	0	0	0	0
Severe Exacerbations								
Total	4	3	3	7	5	6	0	7
Number of home visits	0	0	0	0	1	0	0	0
Number of physician visits	0	1	1	2	5	6	0	7
Number of urgent/ outpatient visits	0	1	1	0	1	1	0	0
Number of ED visits	2	2	1	1	1	1	0	3
Number of in-patient hospital days (ICU)	1	0	4	5	30	12	0	23
Number of in-patient hospital days (ward)	33	33	20	45	55	64	0	50

ED = emergency department; FF = fluticasone furoate; FF/V = fluticasone furoate + vilanterol; FVC = forced vital capacity; ICU = intensive care unit; NR = not reported; V = vilanterol.

TABLE 44: DETAILED EXACERBATION DATA (VILANTEROL-CONTROLLED STUDY)

	Study 2871		Study 2970	
	FF/V 100/25 N = 403	V25 N = 409	FF/V 100/25 N = 403	V25 N = 409
Moderate Exacerbations				
Total	[redacted]	[redacted]	[redacted]	[redacted]
Number of home visits	[redacted]	[redacted]	[redacted]	[redacted]
Number of physician visits	[redacted]	[redacted]	[redacted]	[redacted]
Number of urgent/outpatient visits	[redacted]	[redacted]	[redacted]	[redacted]
Number of ED visits	[redacted]	[redacted]	[redacted]	[redacted]
Number of in-patient hospital days (ICU)	[redacted]	[redacted]	[redacted]	[redacted]
Number of in-patient hospital days (ward)	[redacted]	[redacted]	[redacted]	[redacted]
Severe Exacerbations				
Total	[redacted]	[redacted]	[redacted]	[redacted]
Number of home visits	[redacted]	[redacted]	[redacted]	[redacted]
Number of physician visits	[redacted]	[redacted]	[redacted]	[redacted]
Number of urgent/outpatient visits	[redacted]	[redacted]	[redacted]	[redacted]
Number of ED visits	[redacted]	[redacted]	[redacted]	[redacted]
Number of in-patient hospital days (ICU)	[redacted]	[redacted]	[redacted]	[redacted]
Number of in-patient hospital days (ward)	[redacted]	[redacted]	[redacted]	[redacted]

ED = emergency department; FF/V = fluticasone furoate + vilanterol; ICU = intensive care unit; V = vilanterol.

Subgroups

TABLE 45: MODERATE/SEVERE EXACERBATIONS REPORTED BY VARIOUS SUBGROUPS (VILANTEROL-CONTROLLED STUDIES)

	Study 2871		Study 2970	
	FF/V 100/25 N = 403	V25 N = 409	FF/V 100/25 N = 403	V25 N = 409
Non-Reversible				
LS mean annual rate	[redacted]	[redacted]	[redacted]	[redacted]
Ratio (95% CI)	[redacted]		[redacted]	[redacted]
Reversible				
LS mean annual rate	[redacted]	[redacted]	[redacted]	[redacted]
Ratio (95% CI)	[redacted]		[redacted]	[redacted]
Former Smoker				
LS mean annual rate	[redacted]	[redacted]	[redacted]	[redacted]
Ratio (95% CI)	[redacted]	[redacted]	[redacted]	

	Study 2871		Study 2970	
	FF/V 100/25 N = 403	V25 N = 409	FF/V 100/25 N = 403	V25 N = 409
Current Smoker				
LS mean annual rate	[redacted]	[redacted]	[redacted]	[redacted]
Ratio (95% CI)	[redacted]	[redacted]	[redacted]	

CI = confidence interval; FF = fluticasone furoate; FF/V = fluticasone furoate + vilanterol; LS = least squares; V = vilanterol.
Source: FDA statistical review.

TABLE 46: TROUGH FEV_1 (L) REPORTED BY VARIOUS SUBGROUPS (VILANTEROL-CONTROLLED STUDIES)

	Study 2871		Study 2970	
	FF/V 100/25 N = 403	V25 N = 409	FF/V 100/25 N = 403	V25 N = 409
Non-reversible				
LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. V	[redacted]	[redacted]	[redacted]	
Reversible				
LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. V	[redacted]	[redacted]	[redacted]	
Former smoker				
LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. V	[redacted]		[redacted]	[redacted]
Current smoker				
LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. V	[redacted]		[redacted]	[redacted]

FF/V = fluticasone furoate + vilanterol; LS = least squares; NR = not reported; SE = standard error; V = vilanterol.
Source: FDA statistical review.

TABLE 47: TROUGH FEV_1 (L) REPORTED BY VARIOUS SUBGROUPS (PLACEBO-CONTROLLED STUDIES)

	Study 2206				Study 2207			
	FF/V 100/25 N = 206	Placebo N = 207	FF 100 N = 206	V25 N = 205	FF/V 100/25 N = 204	Placebo N = 205	FF 100 N = 204	V25 N = 203
Non-Reversible								
LS mean (SE) day 169	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. placebo	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Study 2206				Study 2207			
	FF/V 100/25 N = 206	Placebo N = 207	FF 100 N = 206	V25 N = 205	FF/V 100/25 N = 204	Placebo N = 205	FF 100 N = 204	V25 N = 203
Reversible								
LS mean (SE) day 169	[redacted]							
Difference vs. placebo	[redacted]							
Current Smoker								
LS mean (SE) day 169	[redacted]							
Difference vs. placebo	[redacted]							
Former Smoker								
LS mean (SE) day 169	[redacted]							
Difference vs. placebo	[redacted]							

FF = fluticasone furoate; FF/V = fluticasone furoate + vilanterol; LS = least squares; SE = standard error; V = vilanterol.
Source: FDA statistical review.

TABLE 48: FEV_1 0 TO 24 HOURS BY VARIOUS SUBGROUPS (FLUTICASONE PROPIONATE PLUS SALMETEROL-CONTROLLED STUDIES)

	Study 3107		Study 3109		Study 2352		Study 6974	
	FF/V 100/25 N = 266	FP/S 500/50 N = 262	FF/V 100/25 N = 260	FP/S 250/50 N = 259	FF/V 100/25 N = 259	FP/S 250/50 N = 252	FF/V 100/25 N = 412	FP/S 250/50 N = 416
Non-Reversible								
LS mean (SE) baseline	[redacted]							
LS mean (SE) change	[redacted]							
LS MD (95% CI)	[redacted]							
Reversible								
LS mean (SE) baseline	[redacted]							

	Study 3107		Study 3109		Study 2352		Study 6974	
	FF/V 100/25 N = 266	FP/S 500/50 N = 262	FF/V 100/25 N = 260	FP/S 250/50 N = 259	FF/V 100/25 N = 259	FP/S 250/50 N = 252	FF/V 100/25 N = 412	FP/S 250/50 N = 416
LS mean (SE) change	[redacted]							
LS MD (95% CI)	[redacted]							
Current Smoker								
LS mean (SE), baseline	[redacted]							
LS mean (SE) change	[redacted]							
LS MD (95% CI)	[redacted]							
Former Smoker								
LS mean (SE) baseline	[redacted]							
LS mean (SE) change	[redacted]							
LS MD (95% CI)	[redacted]							
Age < 65								
LS mean (SE) baseline	[redacted]							
LS mean (SE) change	[redacted]							
LS MD (95% CI)	[redacted]							
Age ≥ 65								
LS mean baseline (SE)	[redacted]							
LS mean (SE) change	[redacted]							
LS MD (95% CI)	[redacted]							
GOLD Stage 2								
LS mean baseline (SE)	[redacted]							
LS mean (SE) change	[redacted]							
LS MD (95% CI)	[redacted]							
GOLD Stage 3								
LS mean (SE) baseline	[redacted]							
LS mean (SE) change	[redacted]							
LS MD (95% CI)	[redacted]							

	Study 3107		Study 3109		Study 2352		Study 6974	
	FF/V 100/25 N = 266	FP/S 500/50 N = 262	FF/V 100/25 N = 260	FP/S 250/50 N = 259	FF/V 100/25 N = 259	FP/S 250/50 N = 252	FF/V 100/25 N = 412	FP/S 250/50 N = 416
GOLD Stage 4								
LS mean baseline (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean (SE) change	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS MD (95% CI)	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; FF/V = fluticasone furoate + vilanterol; FP/S = fluticasone propionate + salmeterol; GOLD = Global Initiative for Chronic Lung Disease; LS = least squares; MD = mean difference; NR = not reported; SE = standard error; V = vilanterol.

APPENDIX 6: VALIDITY OF OUTCOME MEASURES

Aim

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

- Forced expiratory volume in one second (FEV_1)
- Chronic Respiratory Disease Questionnaire self-administered scale (CRQ-SAS)
- St. George's Respiratory Questionnaire (SGRQ).

Findings

FEV_1, CRQ-SAS, and SGRQ are briefly summarized in Table 49.

TABLE 49: VALIDITY AND MINIMAL CLINICALLY IMPORTANT DIFFERENCE OF OUTCOME MEASURES

Instrument	Type	Validated	MCID	References
FEV_1	FEV_1 is the volume of air that, after a full inspiration, can be forcibly expired in one second.	Yes	0.10 L to 0.14 L	45
CRQ-SAS	Self-administered. CRQ-SAS consists of 20 items measuring 4 domains: dyspnea, fatigue, emotional function, and mastery. Patients rated their experience on a 7-point scale, ranging from 1 to 7, where a higher score indicates less severe symptoms or better quality of life.	Yes	0.5 per item	16, 37-39, 46
SGRQ	The SGRQ is a disease-specific measure of HRQoL that consists of 50 items and was specifically developed for patients with chronic airflow limitation. The SGRQ-COPD (SGRQ-C) is a well-established instrument for the assessment of health status in patients with COPD. The questionnaire is divided into 3 dimensions: symptoms, activity, and impacts of the disease. The total score ranges from 0 to 100, where 0 indicates no impairment and 100 indicates worst.	Yes	4.0	47-50

CRQ-SAS = Chronic Respiratory Disease Questionnaire self-administered scale; FEV_1 = forced expiratory volume in one second; HRQoL = health-related quality of life; MCID = minimal clinically important difference; SGRQ = St. George's Respiratory Questionnaire; SGRQ-C = St. George's Respiratory Questionnaire for COPD.

One-Second Forced Expiratory Volume

FEV_1 is the volume of air that, after a full inspiration, can be forcibly expired in one second. It is commonly used both in clinical practice and in clinical trials and is generally thought to correlate with COPD outcomes.[51, 52] In clinical practice, FEV_1 is used to grade risk of death in COPD patients.[53] The generally accepted clinically important change in FEV_1 is between 0.10 L and 0.14 L.[45] There is evidence that for patients who are undergoing COPD exacerbation, a two-day increase of 0.10 L reduces the relative risk of treatment failure by 20%.[51] However, changes of the same magnitude are not always associated with clinically important differences in all studies.

While both pre- and post-bronchodilator FEV_1 values have been reported to be indicators of health status, risk of death, and measure of severity in COPD, the Global Initiative for Chronic Lung Disease (GOLD) criteria indicate that post-bronchodilator values should be used.[53] This is supported by evidence from a prospective study of 300 patients with COPD who were followed for at least one and a half years and who were evaluated every three months until the end of the study.[53] Predictors of mortality were

analyzed. While FEV_1, body mass index (BMI), dyspnea score, and several other factors were shown to be predictors of mortality, multivariate analyses showed that post-bronchodilator per cent-predicted FEV_1 was a significant independent predictor of both all-cause mortality and respiratory-cause mortality; whereas the pre-bronchodilator per cent-predicted FEV_1 was not (all-cause mortality: $P = 0.008$ versus 0.126; respiratory-cause mortality: $P = 0.0016$ versus 0.302). Furthermore, with respect to GOLD classifications of disease severity, the discriminative ability of the GOLD severity classification was higher using post-bronchodilator than with pre-bronchodilator per cent-predicted FEV_1 ($P = 0.009$ versus 0.131).

Normalized AUC FEV_1 is an average of the measurement of bronchodilatation over at least 80% of the duration of action after a single inhalation.[54] No information regarding the validity of this outcome or the MCID was identified.

Chronic Respiratory Questionnaire

The Chronic Respiratory Disease Questionnaire (CRQ) was developed by Guyatt et al. in 1987. CRQ examines four aspects of patients' lives: dyspnea, fatigue, emotional function, and mastery (the feeling of control over the disease and its effects).[55] Originally it was administered by a clinician, but has since been modified to a self-administered scale (CRQ-SAS).[37, 38, 55-58] The CRQ-SAS consists of 20 items that measure physical and emotional function, divided into four dimensions: dyspnea, fatigue, emotion, and mastery. Patients are asked to choose five activities from a list of 25, or can mention other activities that are not on the list. This means that the dyspnea dimension is strictly individualized. When completing CRQ-SAS, patients rate their experience on a 7-point scale, ranging from 1 (maximum impairment) to 7 (no impairment), where a higher score indicates less severe symptoms or better quality of life.[15, 16, 46, 59] The validity, sensitivity, internal consistency, and test–retest reliability were studied and reported for each of the four dimensions.[56-58, 60, 61] The mean change of 0.5 per item was considered as the MCID for dyspnea, fatigue, or emotional function score in patients with COPD.[37-39]

In one study,[55] Guyatt at al. studied the reproducibility tested and responsiveness (sensitivity to change) of CRQ-SAS in 100 patients with chronic airflow limitation. The author concluded the changes in questionnaire score were correlated with changes in spirometric values, exercise capacity, and patients' and physicians' global ratings. Thus, it has been shown that the questionnaire is precise, valid, and responsive.[55] It can therefore serve as a useful disease-specific measure of quality of life for clinical trials. CADTH consulting clinical experts also indicated that the CRQ-SAS used to be frequently applied to assess quality of life in patients with COPD, but it has not been seen in recent years. In 1994, the reliability and validity of the four separate dimensions of the CRQ were investigated by Wijkstra et al.[58] In the study by Wijkstra, the internal consistency and reliability of each dimension of the CRQ was investigated and it was found that items of the fatigue, emotion, and mastery dimensions of the CRQ are reliable and valid and can be used to assess quality of life in patients with severe airway obstruction. Items of the dyspnea dimension are less reliable and should not be included in the overall score of the CRQ in comparative research.[58] However, by scoring the items of dyspnea separately, they may be useful for evaluating the effects of intervention in a specific patient.[58] In another study, [60] the CRQ-SAS and St. George's Respiratory Questionnaire (SGRQ) were compared. It was found that the internal consistency was good for both questionnaires (Cronbach's alpha coefficients > 0.84 for the CRQ and > 0.76 for the SGRQ).[60] It was concluded by the author that since this analysis of reliability, validity, and responsiveness to change did not clearly favour one instrument above the other, the choice between the CRQ and the SGRQ can be based on other considerations, such as the required sample size.[60]

St. George's Respiratory Questionnaire

The SGRQ is a disease-specific measure of health-related quality of life (HRQoL) that consists of 50 items and was specifically developed for patients with chronic airflow limitation.[47] It was developed in 1992 to measure impaired health and perceived well-being in patients with airway disease, and to meet the need for a sensitive measure of HRQoL.[62] The instrument has been used worldwide in studies and in clinical settings.[62] The SGRQ questionnaire includes questions regarding sleep disturbances, public embarrassment, and panic (which can be signs of depression or anxiety), as well as feeling like a nuisance to friends and family, employment, and recreation activities (which are indicative of social impact).[63]

The 50 items of the questionnaire are divided into three dimensions: symptoms (8 items measuring the distress due to respiratory symptoms), activity (16 items measuring the effect of disturbances on mobility and physical activity), and impacts (26 items measuring the psychosocial impact of the disease).[50] Items are weighted using empirically derived weights to determine the total SGRQ, which ranges from 0 to 100, where 0 indicates no impairment and 100 indicates worst possible health.[49, 50] The generally accepted MCID for a change in total SGRQ from baseline is 4.0 units of change, a decrease in scores indicates an increase in HRQoL.[48] These have been examined as within-group measures, not between-group measures. As all estimates of clinical significance are subject to measurement error and sample error and require value judgments, MCID should be interpreted with caution, [48] and it is unclear what between-group MCID would be appropriate.

Component scores for the symptoms, activity, and impact domains can be calculated (also ranging from 0 to 100) in addition to the total score. In the symptoms domain, patients are asked to rate the appearance, frequency, and severity of respiratory symptoms (wheeze, breathlessness, cough, etc.) on a 5-point scale, where the low scores indicate no symptoms and high scores indicate more severe symptoms.[50] A number of items in the symptoms component relate to the frequency of symptoms over the previous year.[64] Responses on the other two domains are mostly yes–no in nature. The activity domain deals with mobility and physical activity problems that either cause or are limited by breathlessness.[50] Impacts covers aspects involved in social functioning, and psychosocial disturbances resulting from obstructive airways disease (employment, panic, medication, and side effects).[50] Social functioning and psychosocial disturbances have been identified by patients as particularly troubling aspects of COPD. The SGRQ-COPD (SGRQ-C) is a well-established instrument for the assessment of health status in patients with COPD.[49] A difference of ≥ 4 points in the SGRQ total score versus placebo at study end, or a ≥ 4 points difference from baseline is considered to be the MCID for this measure.[26]

Summary

FEV_1, SGRQ, and CRQ-SAS have all been shown to be valid outcome measure for patients with COPD. The suggested MCIDs for FEV_1, SGRQ and CRQ-SAS were 0.10 L to 0.14 L, a four-unit change from baseline, and 0.5-point change per item respectively. Because they have similar reliability, validity, and sensitivity, the choice between the CRQ-SAS and the SGRQ (SGRQ-C) were based on other considerations, such as the required sample size; however, while the CRQ-SAS was once frequently used in clinical trials, this has not been the case in recent years.

APPENDIX 7: SUMMARY OF PHARMACOLOGY

Aim

The aim of this summary is to summarize the pharmacology information of Breo Ellipta and compare the pharmacokinetic characteristics reported in its product monograph with the following drugs:

- Fluticasone furoate
- Fluticasone propionate
- Budesonide
- Vilanterol
- Salmeterol
- Formoterol
- Indacaterol.

Findings

The product monographs for Breo Ellipta (fluticasone furoate plus vilanterol), fluticasone propionate, salmeterol, formoterol, and indacaterol were reviewed. The pharmacology information of Breo Ellipta and the pharmacokinetic characteristics reported in product monographs of fluticasone furoate versus fluticasone propionate plus vilanterol (versus other long-acting beta2 receptor agonists [LABAs]) are summarized below.

Pharmacology of Breo Ellipta

Breo Ellipta contains fluticasone furoate (a synthetic corticosteroid) and vilanterol (a selective LABA). The precise mechanism of the effect of fluticasone furoate on COPD symptoms is not known.[65] Corticosteroids have been shown to have a wide range of actions on multiple cell types, such as mast cells and eosinophils, as well as multiple mediators such as histamine and eicosanoids involved in inflammation. The onset of action of Breo Ellipta (as defined by time to an increase in FEV_1 of 100 mL following the initial inhalation) occurred with a median time of 16 minutes for 50% of patients in clinical studies.[65] Both fluticasone furoate and vilanterol act locally in the lung; therefore, plasma levels do not predict therapeutic effect. Fluticasone furoate and its metabolites are eliminated primarily in the feces, accounting for approximately 101% oral doses. Urinary excretion accounted for approximately 1% of the oral doses. Following repeat dose–inhaled administration, the half-life of the plasma-elimination phase averaged 24 hours. Vilanterol was eliminated mainly by metabolism, followed by excretion of metabolites in urine and feces (approximately 70% and 30% of the recovered radioactive dose, respectively). Following single dose–inhaled administration, the half-life of the plasma-elimination phase for vilanterol (mean) was 2.5 hours.[65]

Pharmacokinetics

The pharmacokinetics of fluticasone furoate, fluticasone propionate, budesonide, vilanterol, salmeterol, formoterol, and indacaterol are briefly summarized in Table 50 and Table 51. Overall, the half-life of fluticasone furoate appears longer than that of fluticasone propionate. There is no information reported in the product monograph that compares fluticasone furoate with fluticasone propionate or compares vilanterol with salmeterol, formoterol, or indacaterol directly. Data gathered from healthy patients or patients with COPD were, sometimes, not clearly specified (Table 50 and Table 51). The parameters were reported as median or means and, as such, cannot be directly compared. Therefore, the information provided in the summary provides only a rough overall pharmacokinetic profile, and direct comparisons between the drugs cannot be made from the data provided.

TABLE 50: PHARMACOKINETIC PARAMETERS OF FLUTICASONE FUROATE, FLUTICASONE PROPIONATE, AND BUDESONIDE

	Fluticasone Furoate	Fluticasone Propionate	Budesonide
T_{max} (h)	Median (range): 1.00 (0.08, 3.00)[a]	Mean: 3–4[b]	< 0.5[b,d]
T½ (h) mean	23.7[a]	> 14[b]	2.8–4.0[b]
C_{max} (pg/mL) mean	12.0[c]	NR	NR
AUC (0–24) (pg.h/mL) mean	182.2[c]	NR	NR

AUC = area under the curve; C_{max} = the peak plasma concentration of a drug after administration; COPD = chronic obstructive pulmonary disease; NR = not reported; T_{max} = time to reach C_{max}; $T_{½}$ = biological half-life.
[a] In healthy patients.
[b] Population not specified.
[c] In patients with COPD.
[d] Whether it was reported as mean or median was not specified in the product monograph.
Source: Product monograph.[65-68]

TABLE 51: PHARMACOKINETIC PARAMETERS OF VILANTEROL, SALMETEROL, FORMOTEROL, AND INDACATEROL

	Vilanterol	Salmeterol	Formoterol	Indacaterol
T_{max} (h)	Median: 0.17[a]	NR	Mean: 0.25[c]	NR
T½ (h) mean	2.47[a]	NR	8–9[c]	45.5–126[c]
C_{max} (pg/mL) mean	43.2[c]	230[b]	NR	100[c]
AUC (0–24) (pg.h/mL), mean	265.7[c]	NR	NR	1,150[c]

AUC = area under the curve; C_{max} = The peak plasma concentration of a drug after administration; COPD = chronic obstructive pulmonary disease; NR = not reported; T_{max} = time to reach C_{max}; $T_{½}$ = biological half-life.
[a] In healthy patients.
[b] Population not specified.
[c] In patients with COPD.
Source: Product monographs.[65, 67, 69-74]

Summary

Breo Ellipta contains fluticasone furoate (a synthetic corticosteroid) and vilanterol (a selective LABA). The precise mechanism of the effect of fluticasone furoate on COPD symptoms is not known.[65] The half-life of fluticasone furoate appears longer than fluticasone propionate. There is no information reported in the product monograph that compares fluticasone furoate with fluticasone propionate or budesonide, or compares vilanterol with salmeterol, formoterol, or indacaterol directly. Therefore, the information presented here provides only a rough overall pharmacokinetic profile of fluticasone furoate versus fluticasone propionate, or vilanterol versus other LABAs.

APPENDIX 8: SUMMARY OF DRY POWDER INHALERS

Aim

The aim of this summary is to describe the characteristics regarding ease of use and correct use, as well as patient satisfaction, for the Breo Ellipta inhaler device, Advair DISKUS, and Spiriva HandiHaler used in the patients with chronic obstructive pulmonary disease (COPD).

Findings

The characteristics of the dry powder inhaler are summarized below.

Characteristics of the Inhalers

Breo Ellipta is delivered with the Ellipta device, a multi-dose dry powder inhaler. Ellipta holds two double-foil strips of sealed dry powder formulation: one containing the inhaled corticosteroid (ICS; fluticasone furoate 100 mcg), the other containing the long-acting beta-agonist (LABA; vilanterol 25 mcg). A nominal blister content of fluticasone furoate plus vilanterol 100/25 mcg delivers a dose of 92/22 mcg to the patient.[75] The inhaler comes with preloaded multi-doses of Breo Ellipta. To load a single dose into the chamber for use, the patient must open the cover of the inhaler fully, which is confirmed by a clicking sound and shown by a decrease in the number on the counter. After inhaling, the patient may not taste or feel the medicine, even when using the inhaler appropriately; there is no indicator that tells a patient the dose has been properly delivered or inhaled.[76]

Advair is delivered with the Advair DISKUS, a multi-dose dry powder inhaler.[77] Advair DISKUS holds a foil strip of sealed dry powder containing a formulation of fluticasone propionate and salmeterol xinafoate.[77] The patient take Advair DISKUS out of the foil pouch just before using it for the first time. The inhaler comes with preloaded multi-doses of Advair. To load a single dose for use, the patient must slide the lever of the inhaler fully, which is confirmed by a clicking sound and shown by a decrease in the number on the counter. After inhaling, the patient may not taste or feel the medicine, even when using the inhaler appropriately; there is no indicator that tells a patient the dose has been properly delivered or inhaled.[77] After breathing in the medicine, patients are required to rinse their mouth with water and spit it out.[77]

Tiotropium bromide is delivered via the HandiHaler.[78] The patient must open the dust cap, open the mouth piece, remove a capsule from a blister package, place the capsule in the inhaler, push and release a button to crush the capsule, fully exhale, then inhale the dry powder. To ensure the full dose is achieved, the patient must then fully exhale and inhale any remaining dry powder. There is no indicator that tells a patient the dose has been properly loaded and is ready to inhale, but the patient should be able to hear the capsule vibrating, an indicator that the dose has been properly inhaled.

More details regarding the characteristics of each inhaler are included in Table 52.

TABLE 52: INHALER CHARACTERISTICS

Characteristic	NDPI (Breo Ellipta)[76, 79]	Advair DISKUS[77]	Spiriva HandiHaler[78, 80]
Preloaded/ Multi-dose	Yes — multiple doses come loaded in inhaler. Patient opens the cover of the inhaler fully to load a dose.	Yes — multiple doses come loaded in inhaler. Patient opens the cover of the inhaler fully to load a dose.	No — patient must remove tablet from blister package and insert into inhaler.[a]
Confirmation that dose is ready	Auditory — a clicking sound indicates a dose is ready to be inhaled. This is also shown by a decrease in the number on the counter.	Auditory — a clicking sound indicates a dose is ready to be inhaled.	No — auditory click indicates mouthpiece has been properly secured, but nothing indicates dose is ready.
Confirmation of dose delivery	No audible or visible sign. Dose delivery is based on inhaling correctly. Patients may not taste or feel the medicine. If patients open and close the cover without inhaling the medicine, they will lose the dose.	No audible or visible sign. Dose delivery is based on inhaling correctly.	Yes — can hear and feel capsule vibrate in the device chamber; may taste sweet.
Number of inhalations required	1, once daily	1, twice daily	2, once daily
Requires step after inhalation	No	No	Yes — must remove used capsule from the chamber after use.
Inhaler requires cleaning	Routine cleaning is not required. Can clean the mouthpiece if needed, using a dry tissue, before closing the cover.	The DISKUS must not be washed.	Once per month

NDPI = novel dry powder inhaler.
[a] Requires patient to peel the outer foil off the package, not push pill through the package.

Patient Use of Inhalers

It was reported that in clinical trials, 98% of patients used Ellipta correctly following a single instruction.[36, 81, 82] Based on recall, 59% to 65% of patients with COPD preferred Ellipta over the HandiHaler device. In an exploratory exit survey of patient preference from phase 3 studies, 95% of patients preferred the Ellipta device to HandiHaler, and 86% of patients preferred the Ellipta device over DISKUS.[83] A direct link between Breo Ellipta and improved adherence has not been established, but it was suggested that a preference for a particular inhaler device may be associated with improved adherence to a therapeutic regimen.[84]

Limitations

The primary limitation of the patient satisfaction and ease-of-use studies is that they were sponsored by manufacturers. Furthermore, the investigators were not blinded to the inhalers being used. No information was provided regarding comorbid conditions that may affect the use of the devices, such as arthritis or cognitive difficulties.

Summary

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

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