Common Drug Review
Clinical Review Report

February 2016

Drug	Fluticasone furoate/vilanterol (Breo Ellipta)
Indication	Once-daily maintenance treatment of asthma in patients aged 18 years and older with reversible obstructive airways disease
Listing request	As per indication
Dosage form(s)	Dry powder for oral inhalation, 100/25 and 200/25 mcg
NOC date	August 5, 2015
Manufacturer	GlaxoSmithKline

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Figure

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies 17

ABBREVIATIONS

ACT	Asthma Control Test
AE	adverse event
ANCOVA	analysis of covariance
AQLQ	Asthma Quality of Life Questionnaire
AQLQ +12	Asthma Quality of Life Questionnaire for 12 years and older
AUC	area under the curve
BCLA	British Columbia Lung Association
BDP	beclomethasone dipropionate
BUD	budesonide
CI	confidence interval
CDR	CADTH Common Drug Review
CrI	credible interval
FEV_1	forced expiratory volume in one second
F	formoterol fumarate dihydrate
FF	fluticasone furoate
FP	fluticasone propionate
HRQoL	health-related quality of life
ICS	inhaled corticosteroid
IDC	indirect comparison
ITT	intention-to-treat population
LABA	long-acting beta2-agonist
LAMA	long-acting muscarinic antagonist
LOCF	last observation carried forward
LS	least squares
MCID	minimal clinically important difference
MPPI	minimal patient perceivable improvement
MOM	mometasone furoate
NMA	network meta-analysis
OLA	Ontario Lung Association
PEF	peak expiratory flow
PP	per-protocol
QoL	quality of life
RCT	randomized controlled trial
S	salmeterol
SABA	short-acting beta2-agonist
SAE	serious adverse event
VI	vilanterol
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Asthma is a common chronic respiratory disorder characterized by reversible airway obstruction, pulmonary inflammation, airway hyper-responsiveness, and airway remodelling.[1,2] Symptoms include wheezing, dyspnea, chest tightness, sputum production, and coughing.[2] It is estimated that 2.4 million Canadians aged 12 and older have a diagnosis of asthma.[3]

Breo Ellipta is a once-daily, single inhalation, fixed-dose combination of an inhaled corticosteroid (ICS) (fluticasone furoate [FF]) and a long-acting beta2-agonist (LABA) (vilanterol [VI]). FF is a synthetic, long-acting corticosteroid with potent anti-inflammatory properties that inhibit inflammatory cell functions, while VI stimulates beta2 receptors, resulting in long-acting bronchodilator effects on the bronchi. Breo Ellipta has received a Health Canada indication for once-daily maintenance treatment of asthma in patients aged 18 years and older with reversible obstructive airways disease, and the manufacturer is seeking reimbursement in line with this indication. The product monograph for Breo Ellipta further states that Breo Ellipta is "**not** indicated for patients whose asthma can be managed by occasional use of a rapid onset, short duration, inhaled beta2-agonist or for patients whose asthma can be successfully managed by ICSs along with occasional use of a rapid onset, short duration, inhaled beta2-agonist" and is "**not** indicated for the relief of acute bronchospasm."[4] Breo Ellipta (100/25 mcg) is also approved for the long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease. It is available as a dry powder for oral inhalation using the Ellipta inhaler, with each actuation delivering FF/VI at a dose of 200/25 mcg or 100/25 mcg.

The objective of this report was to perform a systematic review of the beneficial and harmful effects of FF/VI for the once-daily maintenance treatment of asthma in patients aged 18 years and older with reversible obstructive airways disease. Key efficacy outcomes of interest included incidence of acute asthma exacerbations, changes in quality of life (QoL), changes in pulmonary function, and impact on health care resource use. Harms outcomes of interest included serious adverse events (SAEs), withdrawals due to adverse events (WDAEs), and total adverse events.

Results and Interpretation

Included Studies

Seven manufacturer-sponsored, phase 3, multi-centre, randomized, double-blind trials met the inclusion criteria for this systematic review: HZA-827 (N = 610), HZA-863 (N = 1,039), HZA-714 (N = 313), HZA-829 (N = 586), HZA-091 (N = 806), HZA-837 (N = 2020), and HZA-839 (N = 503). The trials included patients ≥ 12 years of age diagnosed with asthma, who had a forced expiratory volume in one second (FEV_1) reversibility of ≥ 12% and ≥ 200 mL following albuterol inhalation and who were on ICS, with or without a LABA, for ≥ 12 weeks before screening, with a stable dose maintained for ≥ four weeks. The mean age of trial participants ranged from 38.1 years to 48.8 years, with a majority of females. Study participants had, on average, a history of asthma for more than 10 years. Baseline pre-bronchodilator FEV_1 ranged from 1.646 L to 2.353 L; the smallest FEV_1 was recorded for study HZA-714 (1.646 L to 1.669 L) and the largest was recorded in study HZA-839 (2.290 L to 2.353 L). Per cent predicted pre-bronchodilator FEV_1 at screening ranged from 62.3% to 75.2%, with the smallest values recorded in studies HZA-863 (61.1% to 62.1%) and HZA-829 (63.0% to 63.6%). According to the clinical expert consulted on this review, the patients studied in these trials represent a typical patient population for asthma treatment with an ICS/LABA combination inhaler in Canadian practices (i.e., uncontrolled on an ICS alone).

Six trials evaluated the superiority of one or both fixed doses of FF/VI (100/25 mcg or 200/25 mcg) against fluticasone propionate/salmeterol (FP/S), FF, FP, and/or placebo over a double-blind duration between 12 weeks and 76 weeks. The remaining trial, HZA-839, was a safety and tolerability study evaluating both fixed doses of FF/VI and FP 500 mcg twice daily. All seven trials recruited adults and adolescents, and did not pre-specify any subgroup analysis by age. It is uncertain whether any important differences in treatment effects with FF/VI exist for patients aged < 18 years versus those ≥ 18 years. In the majority of the trials that primarily evaluated lung function, the percentage of adolescents participating in each study group was relatively low (1% to 17%). However, the percentage of adolescents participating in studies HZA-827, HZA-837, and the safety study HZA-839 exceeded 10%. It remains unclear if including adolescents could have potentially biased the efficacy and safety findings.

Efficacy

Study HZA-837 was the only included study designed specifically to evaluate the effects of FF/VI on acute asthma exacerbations. The study was event driven and enrolled patients who had experienced at least one exacerbation in the previous year. Rates of exacerbation per patient per year were 0.14 for the FF/VI 100/25 mcg once daily and 0.19 for FF 100 mcg once-daily treatment groups. This corresponds to patients having to take FF/VI for five years before seeing an additional benefit provided by the LABA component. Over the course of the active treatment period, 186 and 256 exacerbations were reported in patients treated with FF/VI and FF respectively; the hazard ratio was 0.795 (95% confidence interval [CI], 0.642 to 0.985; *P* = 0.036). Although this represents a relative risk reduction of 20%, the absolute reduction was only 3.1% (i.e., the adjusted probability of at least one severe asthma exacerbation by 52 weeks was 15.9% for FF and 12.8% for FF/VI). Although the relative and absolute reductions are consistent with those observed in other ICS/LABA studies versus ICS alone,[5] their clinical relevance is uncertain. In the majority of the other trials, the frequency of severe asthma exacerbation was low, ranging from 0% to 4% within each treatment arm. These trials, which were primarily interested in the impact of treatment on lung function, specifically excluded patients who had experienced an asthma exacerbation within the preceding six months; thus, they represented patients with a lowered risk of experiencing an exacerbation.

Health-related quality of life (HRQoL), as measured using the Asthma Quality of Life Questionnaire for 12 years and older (AQLQ +12), improved in all treatment groups over the course of each study. In nearly all trials, except study HZA-091, the least squares (LS) mean AQLQ +12 score within each treatment arm improved by more than 0.5 points compared with baseline, which represents the commonly accepted minimal clinically important difference (MCID). In most cases, the difference in change in QoL between FF/VI and active comparators at both weeks 12 and 24 could not be compared statistically, as hierarchical testing was stopped before this outcome. The only appropriate statistical tests as per the pre-specified analysis plan were done in studies HZA-863 and HZA-829, in which no statistically significant improvement in QoL emerged between FF/VI and FF 100 mcg or between FF/VI and FF 200 mcg or FP 500 mcg. In addition, patients rated their asthma control as improved by 12 weeks or 24 weeks, as assessed using the Asthma Control Test (ACT). However, per the pre-specified analysis plan, only statistical testing was appropriate in study HZA-863. Patients on FF/VI 100/25 mcg once daily reported a statistically significantly greater improvement in ACT scores than did patients on FF 100 mcg once daily (LS mean change 0.9 points; 95% CI, 0.3 to 1.5; *P* = 0.002). This difference is unlikely to be clinically meaningful (MCID = 3.0 points).

In terms of lung function, the following observations could be made:

- **FF/VI 100/25 mcg versus FF 100 mcg:** Three studies reported that the treatment difference in evening trough FEV_1 ranged from 36 mL to 89 mL at week 12, which was statistically significant in two trials but not in the third.
- **FF/VI 200/25 mcg versus FF 200 mcg:** The mean between-group difference in trough FEV_1 was reported to be 193 mL at week 24 (95% CI, 108 to 277; $P < 0.001$).
- **FF/VI 200/25 mcg versus FP 500 mcg:** One study reported a statistically significant increase in trough FEV_1 at week 24 (mean between-group difference: 210 mL [95% CI, 127 to 294]; $P < 0.001$).
- **FF/VI 100/25 mcg versus FF/VI 200/25 mcg:** At 12 weeks of treatment, trough FEV_1 values were 16 mL greater in high-dose FF/VI than in the moderate dose FF/VI (95% CI, –46 to 77 mL).
- **FF/VI 100/25 mcg versus FP/S 250/50 mcg:** At 24 weeks, the mean difference in evening trough FEV_1 was –19 mL (95% CI, –73 to 34) in FF/VI compared with FP/S.

Given that the literature on MCID for changes in FEV_1 is limited, the clinical importance of the comparisons that were statistically significant with respect to the outcome of trough FEV_1 remains uncertain. Overall, the findings for trough FEV_1 were similar to weighted mean FEV_1.

Few studies looked at the difference in health care resource consumption between treatment groups; overall, the reported average use of health care resources was very low. According to the clinical expert consulted as part of this review, this may in part reflect the fact that patients with asthma typically only seek health care when an exacerbation occurs and, in the trials that collected resource consumption, these patients were at lowered risk of severe exacerbation.

In the absence of adequate head-to-head trial data for FF/VI compared with other combination therapies, and given that a limited number of outcomes were studied in the manufacturer-sponsored study, HZA-091, an indirect treatment comparison (IDC) was conducted based on a systematic review of randomized controlled trials (RCTs) to compare the efficacy of FF/VI against other fixed-dose combination therapies for asthma. The manufacturer's interpretation of the IDC was that FF/VI is broadly comparable to other combination therapies across outcomes for peak expiratory flow (PEF), FEV_1, AQLQ results, and rates of moderate or severe exacerbation. The extent to which this interpretation is valid is highly questionable given considerable concerns about the limited reporting and questionable validity in the methods undertaken to conduct the network meta-analysis (NMA). Furthermore, the Bayesian hierarchical NMA model is likely to be biased due to important clinical and methodological heterogeneities among the included trials.

In the manufacturer's submission to the CADTH Common Drug Review (CDR), claims were made that patients prefer the Ellipta inhaler, and that its once-daily administration can improve adherence over a twice-daily dosing administration. However, no robust direct evidence was available to substantiate these claims. In the single submitted trial that compared FF/VI with FP/S, adherence rates were similarly high between the groups, which would not be unexpected in a clinical trial setting.

Harms

The incidence of adverse events (AEs) in patients treated with FF/VI was similar to those treated with monotherapy (FF, FP) and combination therapy (FP/S). SAEs were rare (< 7% across studies), and did not suggest any association with specific treatments. Three deaths were recorded during study HZA-837: two during the double-blind period, one in each treatment group, and one in the post-treatment follow-up in the FF group. They were all considered non–asthma related.

The most common AEs reported in any treatment group and across all studies were headache, upper respiratory tract infection, and nasopharyngitis. On-treatment infections and infestations were frequent, ranging from 11% to 46%, but were similar across treatment groups within each study. Rates were higher in trials with longer study durations.

Harms were not analyzed in the IDC. With the exception of one study that directly compared FF/VI with FP/S, the comparative safety between FF/VI and other commonly prescribed, fixed-dose, single-inhaler combination therapies (e.g., budesonide/formoterol fumarate dihydrate [BUD/F] and mometasone furoate/formoterol fumarate dihydrate [MOM/F]) is unknown. Long-term (> 52 weeks) safety data for FF/VI are currently unavailable.

Potential Place in Therapy

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

Breo Ellipta is the fourth single-inhaler combination therapy containing an ICS and LABA to be approved by Health Canada for chronic asthma. These combination inhalers are indicated for patients with diagnosed asthma[2,6] who are not successfully controlled by an ICS (at least at a low dose) along with the occasional use of a rapid onset, short-acting beta2-agonist (SABA). FF/VI has overall demonstrated efficacy versus placebo and ICS alone in this population, with statistically significant improvements in lung function and reduced exacerbations. After asthma diagnosis, identification of patients with uncontrolled asthma is based mostly in general practice on symptoms and frequency of SABA use.

The direct and indirect evidence for the comparative benefit of FF/VI versus other ICS/LABA combinations is limited. The manufacturer has also submitted some literature showing that a once-daily ICS increases adherence in patients with asthma when compared with a twice-daily ICS.[7] However, the differences expected in a clinical setting are likely small, and there is no direct evidence that once-daily therapy with FF/VI confers a clinically significant advantage over other ICS/LABA combination inhalers with twice-daily administration in patients with uncontrolled asthma. FF/VI is available in two doses (i.e., moderate and high doses of the ICS component based on equivalent FP); thus, it does not seem to cover the lower-dose ICSs. Guidelines for the management of asthma, based on evidence from systematic reviews and RCTs, recommend that patients 12 years of age and over not achieving asthma control on a low dose of ICS benefit more from combination therapy with LABA than from increasing the maintenance dose of ICS.[2] Therefore, there is uncertainty as to the place in therapy for FF/VI when switching these patients, given that there may not be a want or need to increase to an equivalent moderate dose of ICS (i.e., the FF 100 mcg component). In addition, FF/VI cannot be used as both maintenance and rescue medication, unlike certain other ICS/LABA combinations, such as BUD/F.[2,6]

Conclusions

This analysis included seven double-blind RCTs that recruited patients ≥ 12 years of age with asthma who were inadequately controlled on ICS therapy, in which one or both dosages of FF/VI were compared against equivalent moderate- or high-dose ICS monotherapies (i.e., FF, FP), ICS/LABA combination therapy (i.e., FP/S), or placebo for a minimum of 12 weeks and up to a maximum of 76 weeks. There is very limited comparative evidence for FF/VI versus alternative ICS/LABA combination therapies. FF/VI was not statistically significantly superior to FP/S with respect to lung function. An NMA was provided by the manufacturer comparing FF/VI with the other ICS/LABA combination products; however, given the number of methodological and reporting issues present, the validity of the findings

is highly uncertain. Therefore, the results show unclear comparative clinical benefit of FF/VI against other combination therapies.

Overall, FF/VI was statistically significantly superior to ICS monotherapy in reducing exacerbations among patients at higher risk for exacerbations, and for improving lung function (FEV_1 and PEF), although the evidence base was not considered robust and was of uncertain clinical significance. There was very little evidence to compare the effects of two doses of FF/VI on relevant outcomes. Also, the moderate to high doses of ICS used in the studies means that caution should be used when extrapolating the findings to patients uncontrolled on low-dose ICS. Moreover, there was no clear evidence for improved HRQoL or treatment adherence; there was limited evidence of uncertain clinical significance with respect to symptom improvement; and there was no evidence of reduction in health care resource use or days of missed work or school.

FF/VI appears to have a similar harms profile to the other ICS/LABA comparators, although longer-term comparative studies are needed to elucidate the harms of FF/VI beyond 52 weeks of exposure.

TABLE 1: SUMMARY OF RESULTS — EFFICACY STUDIES

Outcome	HZA-827 (12 weeks)			HZA-863 (12 weeks)			HZA-714 (12 weeks)		HZA-829 (24 weeks)			HZA-091 (24 weeks)		HZA-837 (24 to 76 weeks)	
	FF/VI 100/25 mcg	FF 100 mcg	Placebo	FF/VI 200/25 mcg	FF/VI 100/25 mcg	FF 100 mcg	FF/VI 200/25 mcg	FP 500 mcg	FF/VI 200/25 mcg	FF 200 mcg	FP 500 mcg	FF/VI 100/25 mcg	FP/S 250/50 mcg	FF/VI 100/ 25 mcg	FF 100 mcg
Total, N	202	205	203	346	346	347	157[b]	156[b]	197	194	195	403	403	1,009	1,011
Severe Asthma Exacerbation															
N	201	205	203	346	346	347	155	154	197	194	195	403	403	1,009	1,010
n (%)	1 (< 1)	4 (2)	9 (4)	4 (1)	3 (< 1)	7 (2)	1 (< 1)	3 (2)	0	6 (3)	2 (1)	10 (2)	12 (3)	186 (18)	256 (25)
Time to first severe asthma exacerbation, HR (95% CI)														**0.795 (0.642 to 0.985)**	NA
AQLQ +12															
N	201	201	201	346	345	347	155	154	195	190	193	394	396	Not reported	
Baseline mean (SD)	4.78 (1.00)	4.69 (0.89)	4.78 (1.03)	4.52 (1.07)	4.46 (1.08)	4.50 (1.04)	4.53 (0.93)	4.52 (0.90)	4.37 (0.92)	4.50 (1.00)	4.45 (1.05)	5.35 (1.13)	5.37 (1.13)		
Change from baseline at EOT (SD)	0.85 (0.92)	0.79 (0.91)	0.64 (0.85)	0.97 (1.09)	0.86 (1.08)	0.74 (1.05)	0.80 (0.93)	0.69 (0.90)	0.93 (0.89)	0.92 (0.87)	0.85 (1.03)	0.47 (0.94)	0.36 (0.90)		
LS mean change from baseline (SE)[a]	0.91 (0.06)	0.76 (0.06)	0.61 (0.06)	0.97 (0.05)	0.84 (0.05)	0.76 (0.05)	0.80 (0.07)	0.69 (0.07)	0.93 (0.07)	0.88 (0.07)	0.90 (0.07)	0.46 (0.04)	0.37 (0.04)		
FF/VI vs. monotherapy (95% CI), *P* value	FF 100 mcg: 0.15 (–0.01 to 0.30)[b]			NR	FF 100 mcg: 0.08 (–0.07 to 0.22), *P* = 0.303		FP 500 mcg: 0.12 (–0.08 to 0.32)[b]		FF 200 mcg: 0.05 (–0.14 to 0.24), *P* = 0.587 FP 500 mcg: 0.03 (–0.16 to 0.21)[b]						
FF/VI vs. combination therapy (95% CI), *P* value				FF/VI 100/25 mcg: 0.14 (–0.01 to 0.28)[c]	NR							FP/S 250/50 mcg: 0.09 (–0.03 to 0.21)[b]			
Evening Trough FEV_1 (Absolute Volume), L															
N	201	205	203	346	346	347	Not reported		191	193	194	397	389	1,009	1,010
Baseline mean (SD)	2.344 (0.642)	2.290 (0.617)	2.334 (0.626)	1.954 (0.582)	1.985 (0.556)	1.965 (0.598)			2.129 (0.654)	2.190 (0.676)	2.138 (0.673)	NR	NR	2.216 (0.643)	2.193 (0.640)
LS mean change from baseline (SE) [a]	0.368 (0.030)	0.332 (0.030)	0.196 (0.031)	0.457 (0.022)	0.441 (0.022)	0.365 (0.022)			0.394 (0.030)	0.201 (0.030)	0.183 (0.030)	0.281 (0.019)	0.300 (0.019)	0.337 (0.013)	0.248 (0.013)

Outcome	HZA-827 (12 weeks)			HZA-863 (12 weeks)			HZA-714 (12 weeks)		HZA-829 (24 weeks)			HZA-091 (24 weeks)		HZA-837 (24 to 76 weeks)	
	FF/VI 100/25 mcg	**FF 100 mcg**	**Placebo**	**FF/VI 200/25 mcg**	**FF/VI 100/25 mcg**	**FF 100 mcg**	**FF/VI 200/25 mcg**	**FP 500 mcg**	**FF/VI 200/25 mcg**	**FF 200 mcg**	**FP 500 mcg**	**FF/VI 100/25 mcg**	**FP/S 250/50 mcg**	**FF/VI 100/ 25 mcg**	**FF 100 mcg**
FF/VI vs. monotherapy (95% CI), *P* value	FF 100: 0.036 (–0.048 to 0.120), *P* = 0.405			NR	**FF 100: 0.077 (0.016 to 0.138), *P* = 0.014**				**FF 200: 0.193 (0.108 to 0.277), < 0.001 FP 500: 0.210 (0.127 to 0.294), *P* < 0.001**					**FF 100: 0.089 (0.052 to 0.126), *P* < 0.001**	
FF/VI vs. combination therapy (95% CI), *P* value				FF/VI 100/25: 0.016 (–0.046 to 0.077)[c]	NR							FP/S 250/50: –0.019 (–0.073 to 0.034)[b]			
Evening PEF (L/min)															
N	201	205	203	346	346	347	155	154	197	194	195	Not reported		Not reported	
Baseline mean (SD)	370.2 (122.7)	375.0 (112.8)	367.8 (110.5)	325.7 (111.3)	335.0 (106.7)	344.5 (121.4)	265.2 (95.5)	262.7 (104.9)	342.6 (112.4)	347.8 (120.1)	344.3 (116.1)				
LS mean change from baseline (SE)[a]	26.4 (2.35)	14.1 (2.34)	–1.8 (2.36)	41.7 (2.24)	39.7 (2.24)	15.5 (2.24)	39.1 (3.01)	10.5 (3.03)	39.8 (2.93)	9.1 (2.98)	13.6 (2.96)				
FF/VI vs. monotherapy (95% CI), *P* value	FF 100: 12.3 (5.8 to 18.8)[b]			NR	**FF 100 mcg: 24.2 (18.0 to 30.4); *P* < 0.001**		**FP 500 mcg: 28.5 (20.1 to 36.9); *P* < 0.001**		FF 200 mcg: 30.7 (22.5 to 38.9)[b] FP 500 mcg: 26.2 (18.0 to 34.3)[b]						
FF/VI vs. combination therapy (95% CI)				FF/VI 100/25 mcg: 2.0 (–4.2 to 8.2)[c]	NR										
Use of Rescue Medication															
N (%)	201	205	203	346	346	347	155	154	197	194	195	Not reported		Not reported	
Baseline mean (SD)	13.4 (27.4)	15.3 (29.2)	14.5 (29.9)	5.8 (16.0)	4.4 (12.6)	4.4 (12.1)	10.3 (24.7)	12.4 (27.8)	7.6 (19.2)	7.8 (20.7)	6.3 (18.0)				
LS mean change from baseline (SE)[a]	37.1 (2.3)	26.5 (2.3)	17.8 (2.3)	35.8 (1.9)	34.8 (1.9)	22.6 (1.8)	32.4 (3.0)	31.5 (3.0)	38.2 (2.4)	26.6 (2.5)	31.9 (2.5)				
FF/VI vs. monotherapy	FF 100 mcg: 10.6 (4.3 to			NR	FF 100 mcg: 12.2 (7.1 to		FP 500 mcg: 1.0		FF 200 mcg: 11.7 (4.9, 18.4);						

Outcome	HZA-827 (12 weeks)			HZA-863 (12 weeks)			HZA-714 (12 weeks)		HZA-829 (24 weeks)			HZA-091 (24 weeks)		HZA-837 (24 to 76 weeks)	
	FF/VI 100/25 mcg	FF 100 mcg	Placebo	FF/VI 200/25 mcg	FF/VI 100/25 mcg	FF 100 mcg	FF/VI 200/25 mcg	FP 500 mcg	FF/VI 200/25 mcg	FF 200 mcg	FP 500 mcg	FF/VI 100/25 mcg	FP/S 250/50 mcg	FF/VI 100/ 25 mcg	FF 100 mcg
(95% CI), *P* value	16.8)[b]				17.3), *P* < 0.001		(–7.3 to 9.2), *P* = 0.821		*P* < 0.001 FP 500: 6.3 (–0.4, 13.1), *P* = 0.067						
FF/VI vs. combination therapy (95% CI), *P* value				0.9 (–4.2 to 6.1)[c]	NR										
Safety Outcomes															
Adverse events, N (%)	59 (29)	52 (25)	43 (21)	123 (36)	127 (37)	127 (37)	40 (26)	41 (27)	92 (47)	90 (46)	97 (50)	213 (53)	198 (49)	636 (63)	652 (65)
SAEs, N (%)	0	1 (< 1)	0	1 (< 1)	4 (1)	3 (< 1)	1 (< 1)	2 (1)	6 (3)	1 (< 1)	2 (1)	4 (< 1)	5 (1)	41 (4)	29 (3)
WDAEs, N (%)	2 (< 1)	0	1 (< 1)	3 (< 1)	3 (< 1)	4 (1)	2 (1)	2 (1)	7 (4)	3 (2)	2 (1)	6 (1)	8 (2)	16 (2)	19 (2)
Infections and infestations	34 (17)	31 (15)	22 (11)	66 (19)	62 (18)	71 (20)	26 (17)	25 (16)	59 (30)	61 (31)	70 (36)	124 (31)	112 (28)	461 (46)	440 (44)

ANCOVA = analysis of covariance; AQLQ +12 = Asthma Quality of Life Questionnaire for 12 years and older; CI = confidence interval; EOT = end of treatment; FEV_1 = forced expiratory volume in 1 second; FF = fluticasone furoate; FP = fluticasone propionate; HR = hazard ratio; LS = least squares; NA = not applicable; NR = not reported; PEF = peak expiratory flow; S = salmeterol; SAE = serious adverse event; SD = standard deviation; SE = standard error; VI = vilanterol; vs. = versus; WDAE = withdrawals due to adverse events.

[a] ANCOVA model with covariates of baseline value, region, sex, age, and treatment group.

[b] Because of the hierarchical testing procedure to account for multiplicity, statistical significance cannot be concluded in this comparison.

[c] Statistical testing was not done for the comparison of FF/VI 200/25 mcg vs. FF/VI 100/25 mcg.

Note: Statistically significant values are shown in bold.

Source: Clinical Study Reports.[8-13]

TABLE 2: SUMMARY OF RESULTS — SAFETY STUDY

Outcome	HZA-839 (52 weeks)		
	FF/VI 200/25 mcg	FF/VI 100/25 mcg	FP 500 mcg
Total, N	202	201	100
AEs, N (%)	134 (66)	139 (69)	73 (73)
SAEs, N (%)	1 (< 1)	3 (1)	7 (7)
WDAEs, N (%)	3 (1)	5 (2)	6 (6)
Infections and infestations	72 (36)	87 (43)	46 (46)

AE = adverse event; FF = fluticasone furoate; FP = fluticasone propionate; SAE = serious adverse event; VI = vilanterol; WDAE = withdrawals due to adverse event.

Source: Clinical Study Report.[14]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Asthma is a common chronic respiratory disorder characterized by reversible airway obstruction, pulmonary inflammation, airway hyper-responsiveness, and airway remodelling.[1,2] Described by a range of heterogeneous phenotypes, symptoms may differ by presentation, etiology, and pathophysiology. Patients with asthma typically present with paroxysmal or persistent symptoms of wheezing, dyspnea, chest tightness, sputum production, and coughing that are associated with airflow limitation and airway hyper-responsiveness to endogenous and exogenous stimuli (e.g., exercise, viral respiratory infections, or exposure to certain allergens, irritants, or gases).[2] Although asthma can be diagnosed at any age, it often starts in childhood. In 2015, Statistics Canada estimated that 2.4 million Canadians aged 12 and older had a diagnosis of asthma,[3] representing 12% of all Canadian children and 8% of all Canadian adults.[3]

1.2 Standards of Therapy

Given its heterogeneous phenotypes, the treatment for asthma is individualized to each patient's unique circumstances and customized as necessary. The primary goals in asthma management include long-term maintenance of asthma control[2] with the least amount of medication and minimization of adverse events (AEs).[15] Asthma control, in the Canadian Thoracic Society guidelines, is based on several characteristics, including:

- Frequency of daytime and nighttime symptoms
- Frequency of exacerbations
- Frequency of absences from work or school due to asthma
- Ability to complete normal physical activity
- The need for a fast-acting beta2-agonist
- Forced expiratory volume in one second (FEV_1) or peak expiratory flow (PEF)
- PEF diurnal variation
- Sputum eosinophils.[2]

Asthma control may prevent or minimize the risks of short- and long-term complications, further morbidity, and death.[2] It has been reported that much of asthma-related morbidity is associated with poor management from under-use or poor adherence to maintenance therapy.[16]

According to the guidelines published by the Canadian Thoracic Society, a stepwise approach to pharmacological therapy is recommended to achieve and maintain asthma control.[2] This involves escalating pharmacological treatment, as necessary, to gain control (i.e., step up) and then reducing treatment (i.e., step down) to the minimum required with respect to dose and number of medications for maintenance.[2] Current Canadian and international guidelines recommend that patients with asthma in all age groups be initiated with low-dose inhaled corticosteroids (ICS).[2,17] If control is not gained or maintained, second-line drugs may be added, such as a long-acting beta2-agonist (LABA) or leukotriene receptor antagonist; or the ICS dose can be titrated upward.[2] Table 3 provides a list of ICS/LABA fixed-dose combinations available in Canada. A Cochrane systematic review in 2011 found that the combination of ICS/LABA was superior to ICS and long-acting leukotriene antagonists on all outcomes examined (i.e., risk of exacerbation requiring oral corticosteroids, health-related quality of life [HRQoL], rescue medication-free days, symptom-free days, and improvements in PEF) among patients aged 12 years and older.[5] However, concerns remain with the use of LABAs, given the increased risk of asthma-related deaths and severe exacerbations that have been reported; LABAs are not recommended as

monotherapy for asthma.[2] For individuals whose asthma remains uncontrolled on ICS/LABA, further increases in ICS dose or the addition of leukotriene receptor antagonists or anti-immunoglobulin E (IgE) monoclonal antibodies are recommended.

1.3 Drug

Breo Ellipta is a once-daily, single inhalation, fixed-dose combination of an ICS (fluticasone furoate [FF]), and a LABA (vilanterol [VI]). The fixed-dose combination of FF and VI (FF/VI) is available as a dry powder for oral inhalation using the Ellipta inhaler, with each actuation delivering FF/VI at a dose of 200/25 mcg or 100/25 mcg.

FF has been approved by Health Canada as a single ingredient product for the treatment of asthma; VI does not currently have Health Canada approval as an individual product for any indication.

FF/VI was reviewed by the CADTH Canadian Drug Expert Committee (CDEC) in August 2014 for long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease and received a recommendation to be listed with criteria and condition. Since then, FF/VI has received approval by Health Canada for the indication of once-daily maintenance treatment of asthma in patients aged 18 years and older with reversible obstructive airways disease. The product monograph specifies that FF/VI is "**not** indicated for patients whose asthma can be managed by occasional use of a rapid onset, short duration, inhaled beta2-agonist or for patients whose asthma can be successfully managed by ICSs along with occasional use of a rapid onset, short duration, inhaled beta2-agonist" and is "**not** indicated for the relief of acute bronchospasm."[4] The manufacturer is presently requesting that FF/VI be reimbursed in line with the Health Canada indication for asthma.

Indication under review
Once-daily maintenance treatment of asthma in patients aged 18 years and older with reversible obstructive airways disease
Listing criteria requested by sponsor
As per indication

TABLE 3: KEY CHARACTERISTICS OF FIXED-DOSE COMBINATION THERAPIES WITH INHALED CORTICOSTEROIDS AND LONG-ACTING BETA2-AGONISTS

	Fluticasone propionate/ salmeterol (Advair)	Budesonide/ formoterol fumarate dihydrate (Symbicort)	Mometasone furoate/ formoterol fumarate dihydrate (Zenhale)	Fluticasone furoate/ vilanterol (Breo Ellipta)
Mechanism of action	ICS: anti-inflammatory effects LABA: stimulation of beta2 in the lungs leads to bronchodilation			
Indication[a]	Maintenance treatment of asthma in patients with reversible obstructive airways disease	Treatment of asthma in patients aged 12 years and older with reversible obstructive airways disease	Treatment of asthma in patients 12 years and older with reversible obstructive airway disease	Maintenance treatment of asthma in patients 18 years and older with reversible obstructive airways disease

	Fluticasone propionate/ salmeterol (Advair)	Budesonide/ formoterol fumarate dihydrate (Symbicort)	Mometasone furoate/ formoterol fumarate dihydrate (Zenhale)	Fluticasone furoate/ vilanterol (Breo Ellipta)
Route of administration	Oral inhalation			
Delivery device	**MDI or DPI**	**DPI**	**MDI**	**DPI**
Nominal dose	100/50 mcg or 250/50 mcg or 500/50 mcg, twice daily	100/6 mcg, or 200/6 mcg, or 400/12 mcg, twice daily	50/5 mcg, 100/5 mcg, or 200/5 mcg, twice daily	100/25 mcg or 200/25 mcg, once daily
Adverse effects/ safety issues	ICS component: • Systemic corticosteroid effects (especially high-dose ICS) • Localized candidiasis LABA component: • Cardiovascular morbidity • Increased risk of asthma-related death			

DPI = dry powder inhaler; ICS = inhaled corticosteroid; LABA = long-acting beta-agonists; MDI = metered dose inhaler.
Source: Product monographs.[4,18-20]
[a] Health Canada indication. All product monographs contained statements of contraindications (not for patients whose asthma can be managed by occasional use of rapid onset, short duration, inhaled beta2-agonist, or patients whose asthma can be successfully managed by ICS along with occasional use of rapid onset, short duration, inhaled beta2-agonist).

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of FF/VI (Breo Ellipta) for the treatment of once-daily maintenance treatment of asthma in patients aged 18 years and older with reversible obstructive airways disease.

2.2 Methods

All submitted trials that were considered pivotal by the manufacturer were included in the systematic review. Phase 3 studies were selected for inclusion based on the selection criteria presented in Table 4.

TABLE 4: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient population	Patients (aged ≥ 18 years) with asthma and reversible obstructive airways disease
Intervention	FF (100 mcg or 200 mcg)/VI (25 mcg); oral inhalation once daily
Comparators	ICSs ± beta2-agonist (i.e., LABA and/or SABA)
Outcomes	**Key efficacy outcomes:** • Incidence of acute exacerbations of asthma • QoL[a] • Pulmonary function[a] (e.g., FEV_1, PEF) • Health care resource utilization (e.g., incidence of hospitalizations, ER visits, physician visits) **Other efficacy outcomes:** • Days of missed work or school • Patient adherence and satisfaction • Use of rescue medication (e.g., per cent of rescue-free 24-hour periods) • Number of asthma symptom-free days • Incidence of dyspnea • Incidence of nocturnal awakening **Harms outcomes:** • Mortality • SAEs • WDAEs • AEs[a] • AEs of particular interest: steroid effects (topical, systemic), cardiovascular effects, infections
Study design	Published and unpublished phase 3 RCTs

AE = adverse event; ER = emergency room; FEV_1= forced expiratory volume in 1 second; FF = fluticasone furoate; ICS = inhaled corticosteroids; LABA = long-acting beta2-agonists; PEF = peak expiratory flow; QoL = quality of life; RCT = randomized controlled trial; SABA = short-acting beta2-agonists; SAE=serious adverse events; VI = vilanterol; WDAE = withdrawal due to adverse events.

[a] Key outcomes identified from the patient input summary.

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

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

(Medical Subject Headings), and keywords. The main search concepts were Breo Ellipta; fluticasone furoate and vilanterol; and asthma.
No methodological filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on September 8, 2015. Regular alerts were established to update the search until the CDEC meeting on January 13, 2016. Regular search updates were also performed on databases that do not provide alert services.

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

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 5, Table 6, and Table 7; excluded studies (with reasons) are presented in APPENDIX 3.

3. RESULTS

3.1 Findings from the Literature

In total, seven trials were identified from the literature search for inclusion (Figure 1). The included studies are summarized in Table 5, Table 6, and Table 7and described in Section 3.2.1. A list of excluded studies is presented in APPENDIX 3.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

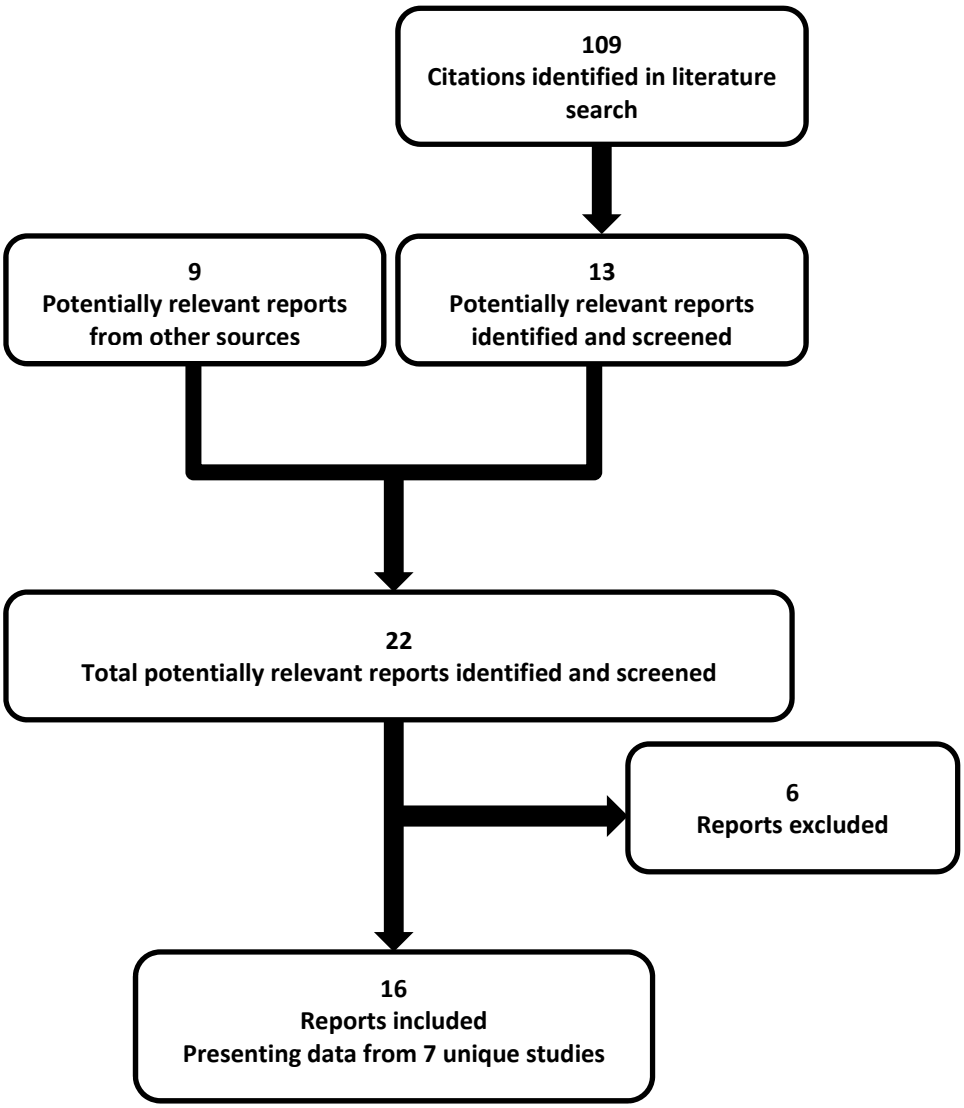

TABLE 5: DETAILS OF INCLUDED STUDIES — LUNG-FUNCTION PROFILE

		HZA-827	HZA-863	HZA-714	HZA-829	HZA-091
DESIGNS & POPULATIONS	**Study design**	DB parallel superiority RCT				
	Locations	Germany, Japan, Poland, Romania, Ukraine, US	Argentina, Chile, Germany, Mexico, Netherlands, Poland, Romania, Russia, Sweden, Ukraine, US	China, Korea, Philippines	Germany, Japan, Poland, Romania, Russia, US	Argentina, Chile, Korea, Netherlands, Philippines, US
	Randomized (N)	610	1,039	313	587	806
	Inclusion criteria	• ≥ 12 years of age, diagnosis of asthma (typically by NIH or GINA) ≥ 12 weeks • Reversibility of FEV_1 ≥ 12% and ≥ 200 mL (at screening visit and end of run-in period) • Current asthma therapy with an ICS (± LABA) ≥ 12 weeks prior to first screening visit; ≥ 4 weeks on stable dose of ICS				
		• Pre-bronchodilator FEV1 of 40% to 90% predicted normal	• Pre-bronchodilator FEV_1 of 40% to 80% predicted normal	• Pre-bronchodilator FEV_1 of 40% to 90% predicted normal • Asian ancestry	• Pre-bronchodilator FEV_1 of 40% to 90% predicted normal	• FEV1 of 40% to 85% predicted normal
		• Mid ICS or low ICS/LABA dose	• Mid to high ICS or mid ICS/LABA dose	• High ICS or mid ICS/LABA dose	• High ICS or mid ICS/LABA dose	• Mid ICS dose
	Exclusion Criteria	• Respiratory infection unresolved within 4 weeks of visit 1 or oral candidiasis • Taking prohibited medication prior to screening (visit 1) or during the study • History of life-threatening asthma, ≥ last 5 years • Asthma exacerbation requiring oral corticosteroids within 12 weeks or overnight hospitalization requiring additional asthma treatment within six months of visit 1 • Current smokers or patients with a smoking history ≥ 10 pack-years • Concurrent respiratory disease or uncontrolled comorbid disease				
		Night shift workers			Night shift workers	Night shift workers
DRUGS	**Intervention**	FF/VI once daily via Ellipta inhaler				
		100/25 mcg	100/25 mcg or 200/25 mcg	200/25 mcg	200/25 mcg	100/25 mcg
	Comparator(s)	Placebo, once daily via Ellipta inhaler FF (100 mcg) once daily via Ellipta inhaler	FF (100 mcg) once daily via Ellipta inhaler	FP (500 mcg) twice daily via Accuhaler inhaler	FF (200 mcg) once daily via Ellipta inhaler FP (500 mcg) twice daily via Accuhaler inhaler	FP/S (250/50 mcg) twice daily via Accuhaler inhaler
DURATION	**Phase**					
	Run-in	4-week		2-week	4-week	
	DB	12-week			24-week	
	Follow-up	2-week	1-week			

		HZA-827	HZA-863	HZA-714	HZA-829	HZA-091
OUTCOMES	**Primary end point**	• Mean change in trough FEV_1 (week 12) • Weighted mean serial FEV_1 over 0 to 24 hours post-dose (week 12)	• Weighted mean serial FEV_1 over 0 to 24 hours post-dose (week 12)	• Mean change in daily p.m. PEF (week 12)	• Mean change in trough FEV_1 (week 24) • Weighted mean serial FEV_1 over 0 to 24 hours post-dose	• Weighted mean serial FEV_1 over 0 to 24 hours post-dose (week 24)
	Secondary end points	• Mean change in percentage of rescue medication-free 24-hour periods during treatment period • Mean change in percentage of symptom-free 24-hour periods during treatment period				• Serial FEV_1 over 0 to 24 hours post-dose (weeks 6, 24) • Time to onset of bronchodilator effect • Weighted mean serial FEV_1 over 0 to 4 hours post-dose (day 1, week 24) • Percentage of participants obtaining ≥ 12% and ≥ 200 mL increase in FEV_1 from baseline • Change in trough FEV_1 (week 24)
		• Mean change in total AQLQ (week 12) • Number of participants who withdrew due to lack of efficacy	• Mean change in trough FEV_1 (week 12) • Mean change in daily a.m. and p.m. PEF (week 12)	• Mean change in daily a.m. PEF (week 12) • Mean change in total AQLQ (week 12)	• Mean change in total AQLQ (week 12,24)	
NOTES	**Publications**	Bleecker, 2014[21]	Bernstein, 2015[22]	Lin, 2015[23]	O'Byrne, 2014[24]	Woodcock, 2013[25]

AE = adverse events; AQLQ = Asthma Quality of Life Questionnaire; DB = double-blind; ED = emergency department; FF = fluticasone furoate; FEV_1= forced expiratory volume in one second; FP = fluticasone propionate; GINA = Global Initiative for Asthma; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist; mcg = microgram; NA = not applicable; NIH = National Institutes of Health; PEF = peak expiratory flow; RCT = randomized controlled trial; SABA = short-acting beta2-agonist; ULN = upper limit of normal; VI = vilanterol.
Note: Two additional reports were included.[26,27]
Source: Clinical Study Reports.[8-12]

TABLE 6: DETAILS OF INCLUDED STUDIES — ASTHMA EXACERBATION

		HZA-837
DESIGNS & POPULATIONS	**Study design**	DB parallel superiority RCT
	Locations	Argentina, Australia, Germany, Japan, Mexico, Philippines, Poland, Romania, Russia, Ukraine, US
	Randomized (N)	2,020
	Inclusion criteria	• Outpatients aged ≥ 12 years of age, diagnosis of asthma by NIH ≥ 1 year • Reversibility of FEV_1 ≥ 12% and ≥ 200 mL • Current asthma therapy with a low to high dose of an ICS or a low to mid dose of an ICS ± LABA ≥ 12 weeks prior to first screening visit; ≥ 4 weeks on stable dose of ICS • Pre-bronchodilator FEV_1 of 50% to 90% predicted normal • History of ≥ 1 asthma exacerbation requiring oral or systemic corticosteroid, ED visit of in-patient hospitalization in previous year
	Exclusion criteria	• Oral candidiasis • Taking prohibited medication prior to screening (visit 1) or during the study • History of life-threatening asthma, ≥ last 5 years • Current smokers or patients with a smoking history ≥ 10 pack-years • Concurrent respiratory disease, or uncontrolled comorbid disease
DRUGS	**Intervention**	FF/VI once daily via Ellipta inhaler
		100/25 mcg
	Comparator(s)	FF (100 mcg) once daily via Ellipta inhaler
DURATION	**Phase**	
	Run-in	2-week
	DB	Min: 24-week Max: 76-week
	Follow-up	NR
OUTCOMES	**Primary end point**	• Time to first severe asthma exacerbation
	Other end points	• Rate of severe asthma exacerbations per patient per year • Change in p.m. trough FEV_1 (week 36)
NOTES	**Publications**	Bateman, 2013[28]

DB = double-blind; ED = emergency department; FEV_1 = forced expiratory volume in 1 second; FF = fluticasone furoate; ICS = inflammatory corticosteroid; LABA = long-acting beta2-agonist; mcg = microgram; NIH = National Institutes of Health; NR = not reported; RCT = randomized controlled trial; VI = vilanterol.
Note: Two additional reports were included.[26,27]
Source: Clinical Study Report.[13]

TABLE 7: DETAILS OF INCLUDED STUDIES — SAFETY AND TOLERABILITY OUTCOMES ONLY

		HZA-839
DESIGNS & POPULATIONS	**Study design**	DB parallel RCT
	Locations	Germany, Thailand, Ukraine, US
	Randomized (N)	503
	Inclusion criteria	• ≥ 12 years of age, diagnosis of asthma by NIH ≥ 12 weeks • Current asthma therapy with a mid to high dose of an ICS ≥ 4 weeks prior to first screening visit • Reversibility of FEV_1 ≥ 12% and ≥ 200 mL (at screening visit and end of run-in period) • FEV_1 ≥ 50% predicted normal • At end of run-in: pupils dilated ≥ 6 mm; LOCS III grades of posterior subcapsular opacity ≤ 0.5, cortical opacity ≤ 2.0, nuclear colour ≤ 3.0, nuclear opalescence ≤ 3.0 at baseline in both eyes; intraocular pressure ≤ 20 mm Hg in both eyes; horizontal cup-to-disc ratio of ≤ 66% in both eyes
	Exclusion criteria	• Oral candidiasis • History of life-threatening asthma, ≥ last 5 years • Asthma exacerbation requiring oral corticosteroids within 12 weeks • Current smokers or patients with a smoking history ≥ 10 pack-years • Concurrent respiratory disease, or uncontrolled comorbid disease
DRUGS	**Intervention**	FF/VI once daily via Ellipta inhaler
		100/25 mcg, 200/25 mcg
	Comparator(s)	FP (500 mcg) twice daily via Accuhaler inhaler
DURATION	**Phase**	
	Run-in	2-week
	Double-blind	52-week
	Follow-up	1-week
OUTCOMES	**Primary end point**	• Number of participants with any AEs or SAEs • Number of severe asthma exacerbations
	Other end points	
NOTES	**Publications**	Busse, 2013[29]

AE = adverse event; DB = double-blind; FF = fluticasone furoate; FEV_1 = forced expiratory volume in one second; FP = fluticasone propionate; ICS = inflammatory corticosteroids; LOCS III = Lens Opacities Classification System, Version III; mcg = microgram; NIH = National Institutes of Health; RCT = randomized controlled trial; SAE = serious adverse event; VI = vilanterol.
Note: Two additional reports were included.[26,27]
Source: Clinical Study Report.[14]

3.2 Included Studies

3.2.1 Description of Studies

Seven phase 3 randomized controlled trials (RCTs) met the inclusion criteria (Table 5, Table 6, Table 7). All were multi-centre, multinational, double-blind studies that studied once-daily FF/VI 100/25 mcg and/or 200/25 mcg fixed-dose combinations delivered via the Ellipta device. Among the included trials, five were lung-function studies (HZA-091, HZA-829, HZA-714, HZA-863, HZA-827), while the remaining two were long-term trials focused either on preventing asthma exacerbation (HZA-837) or solely on assessing safety outcomes (HZA-839). All trials involved a run-in period, between two and four weeks in

duration, before randomization into treatment groups. During the run-in period, patients were maintained on a stable-dose ICS drug and discontinued all other asthma-related medications except for short-acting beta2-agonist (SABA) inhalation aerosols, which were provided for as-needed symptom relief.

All lung-function studies were designed as superiority trials, comparing FF/VI against other alternatives. Among them, study HZA-714 was a 12-week RCT focused specifically on patients with Asian ancestry that compared FF/VI 200/25 mcg once daily against fluticasone propionate (FP) 500 mcg twice daily. The other lung-function trials, however, did not restrict patients' ethnicity. Studies HZA-863, HZA-827, and HZA-829 were all three-arm trials that were either 12 weeks in duration (in the case of the first two) or 24 weeks (the latter). These studies differed in terms of the FF/VI dose (e.g., 100/25 mcg in studies HZA-827 and HZA-863 or 200/25 mcg in studies HZA-863 and HZA-829) and the comparators studied (e.g., placebo or monotherapy with FF or FP). Study HZA-091 was a 24-week, two-arm trial that compared FF/VI 100/25 mcg once daily to another combination therapy: FP/salmeterol (S) 250/50 mcg twice daily.

Study HZA-837 was an event-driven trial designed to terminate following 330 events (i.e., first on-treatment severe asthma exacerbation). The study was intended to assess the addition of VI 25 mcg to once-daily FF 100 mcg in terms of reducing asthma exacerbation. The trial duration varied from 24 weeks to 76 weeks. Lastly, study HZA-839 was a 52-week, three-arm study that compared both doses of FF/VI to FP 500 mcg twice daily in order to address safety issues.

Although the clinical trial program included patients older than 12 years, this review will focus on the Health Canada–approved age subgroup: patients aged 18 years or older. In this review, description of the study population (e.g., patient demographics, exposure to study treatment, and patient disposition) will be presented based on the entire study population, as no formal, a priori subgroup analysis was reported within each trial. However, when possible, efficacy and harms data will be specific to the adult subgroup.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

Enrolment in the clinical trial program was similar across studies: all recruited patients had been diagnosed with asthma and were 12 years of age or older, with FEV_1 reversibility of ≥ 12% and ≥ 200 mL following SABA (albuterol) inhalation. The safety trial, HZA-839, further had specific ophthalmologic inclusion criteria. In terms of pre-bronchodilator FEV_1 at screening, studies varied in the range that was accepted: the majority recruited patients with 40% to 90% of the predicted normal value (HZA-829, HZA-827, and HZA-714), although specific cut-offs were: 40% to 80% (HZA-863), 40% to 85% (HZA-091), 50% to 90% (HZA-837), and ≥ 50% (HZA-839) of the predicted normal value. All patients were on ICS, with or without LABA, for at least 12 weeks before screening, with a stable dose achieved for four weeks or more. However, the permitted dose strength during the run-in period varied across trials, ranging from low to high doses of ICS and low to moderate doses of the ICS/LABA combination therapy, as detailed in Table 5, Table 6, and Table 7.

Exclusion criteria common across studies included patients with unresolved respiratory infection or oral candidiasis; concurrent respiratory disease or uncontrolled comorbid disease; current smokers or patients with a smoking history of 10 pack-years or more; those taking prohibited medications; or those with a history of life-threatening asthma for 5 years or more. With the exception of the event-driven study, HZA-837 (the outcomes of which pertained to asthma exacerbation), the majority of trials excluded patients with an asthma exacerbation that required oral corticosteroids within the last 12 weeks or who had an overnight hospitalization requiring additional asthma treatment within the last six months.

b) Baseline Characteristics

In general, trials recruited patients between the mean age of 38.1 years and 48.8 years, with predominantly fewer males (32% to 45%). In most of the lung-function trials, fewer than 11% of the total sampled population were between the ages of 12 years and 18 years, with the exception of study HZA-827 (10.5% to 16.3%). In the exacerbation and safety trials (i.e., HZA 837 and HZA-839, respectively), adolescents within each study arm represented more than 10% of the total population (12.9% to 17.0%). The majority of patients in each of the studies were Caucasian, with the exception of those in study HZA-714, which was specifically conducted in Asian populations. The mean duration of asthma ranged from 11 years to 22 years; study HZA-827 reported the shortest history of asthma (11 years to 13 years), and study HZA-091 reported the longest history (20.7 years to 22 years). All patients had had previous therapy, either with an ICS alone or ICS/LABA combination therapy.

At screening, pre-bronchodilator FEV_1 ranged from 1.646 L to 2.353 L; the smallest volumes were recorded in studies HZA-714 (1.646 L to 1.669 L) and HZA-091 (1.885 L to 1.930 L), while the largest volumes were recorded in study HZA-839 (2.290 L to 2.353 L). The per cent predicted pre-bronchodilator FEV_1 at screening ranged from 62.3% to 75.2%, with the smallest percentages recorded in studies HZA-863 (62.3% to 62.8%) and HZA-829 (63.0% to 63.6%). The per cent predicted pre-bronchodilator FEV_1 was similar between treatment groups in each study and across the trials. FEV_1 reversibility, as a percentage, ranged from 26.4% to 31.1% and was similar between treatment groups in each study and across studies (Table 8). In studies HZA-863 and HZA-839, the majority of patients had not experienced an exacerbation in the past year. In contrast, given the inclusion criteria of study HZA-837, all patients had had at least one or more exacerbation in the past year.

TABLE 8: SUMMARY OF BASELINE CHARACTERISTICS — LUNG-FUNCTION PROFILE

	HZA-827			HZA-863			HZA-714		HZA-829			HZA-091	
	FF/VI 100/25 mcg (n = 201)	FF 100 mcg (n = 205)	Placebo (n = 203)	FF/VI 200/25 mcg (n = 346)	FF/VI 100/25 mcg (n = 346)	FF 100 mcg (n = 347)	FF/VI 200/25 mcg (n = 155)	FP 500 mcg (n = 154)	FF/VI 200/25 mcg (n = 197)	FF 200 mcg (n = 194)	FP 500 mcg (n = 195)	FF/VI 100/25 mcg (n = 403)	FP/S 250/50 mcg (n = 403)
Age, mean years (SD)	40.7 (16.4)	40.4 (16.8)	38.1 (16.5)	46.6 (14.7)	45.9 (16.1)	44.7 (15.9)	46.9 (12.9)	48.8 (13.4)	46.6 (15.1)	44.6 (14.3)	47.3 (14.1)	43.8 (15.9)	41.9 (16.9)
Age, range	12 to 82	12 to 84	12 to 72	12 to 79	12 to 82	12 to 78	13 to 71	15 to 79	14 to 74	12 to 74	12 to 76	12 to 79	12 to 80
% patients ≥ 18 years of age	180 (89.5)	177 (86.3)	170 (83.7)	330 (95.4)	323 (93.4)	321 (92.5)	153 (98.7)	152 (98.7)	189 (95.9)	187 (96.4)	187 (95.9)	372 (92.3)	362 (89.8)
Male, n (%)	85 (42)	79 (39)	92 (45)	122 (35)	141 (41)	148 (43)	59 (38)	68 (44)	81 (41)	81 (42)	79 (41)	159 (39)	158 (39)
Race													
White, n (%)	172 (86)	171 (83)	169 (83)	300 (87)	307 (89)	305 (88)	0	0	165 (84)	165 (85)	162 (83)	242 (60)	232 (58)
Asian, n (%)	16 (8)	16 (8)	19 (9)	2 (< 1)	2 (< 1)	4 (1)	155 (100)	154 (100)	15 (8)	12 (6)	13 (7)	124 (31)	125 (31)
Other, n (%)	13 (6)	18 (8)	15 (7)	43 (12)	37 (11)	38 (11)	0	0	17 (9)	17 (9)	20 (10)	37 (9)	46 (11)
Duration of asthma, mean years (SD)	12 (12)	13 (12)	11 (10)	19.3 (14.7)	17.8 (14.2)	17.9 (13.6)	12.4 (12.9)	13.4 (13.6)	17.0 (13.2)	14.7 (11.9)	14.9 (12.5)	22.0 (15.9)	20.7 (14.5)
Number of Exacerbations in the Past 12 Months (%)													
0	NR			250 (72)	243 (70)	249 (72)	NR		NR			NR	
1	NR			77 (22)	82 (24)	79 (23)	NR		NR			NR	
2	NR			15 (4)	19 (5)	18 (5)	NR		NR			NR	
3	NR			4 (1)	2 (< 1)	1 (< 1)	NR		NR			NR	
4	NR			0	0	0	NR		NR			NR	
> 4	NR			0	0	0	NR		NR			NR	
FEV_1 at Screening													
N	201	203	203	345	346	346	155	154	194	190	193	398	398
Pre-bronchodilator, L (SD)	2.227 (0.605)	2.174 (0.578)	2.277 (0.622)	1.970 (0.581)	1.997 (0.564)	1.990 (0.571)	1.669 (0.424)	1.646 (0.511)	2.017 (0.623)	2.072 (0.643)	2.017 (0.666)	1.885 (0.606)	1.930 (0.632)
% predicted (SD)	67.25 (11.75)	67.04 (11.36)	68.47 (10.51)	62.62 (9.79)	62.82 (10.41)	62.28 (10.75)	63.84 (12.94)	63.07 (12.47)	62.99 (12.34)	63.27 (12.58)	63.59 (12.41)	63.70 (11.74)	64.40 (11.64)
Post-bronchodilator, L (SD)	2.829 (0.770)	2.808 (0.769)	2.875 (0.779)	NR			2.111 (0.533)	2.072 (0.628)	2.585 (0.779)	2.660 (0.814)	2.594 (0.833)	2.376 (0.780)	2.468 (0.804)
FEV_1 Reversibility at Screening[a]													
N	201	203	202	211	226	212	155	154	194	189	192	397	398
Absolute, mL (SD)	603.1	641.9	597.6	516.8	546.7	584.1	441.7	426.5	561.7	583.3	568.0	487.1	536.3

	HZA-827			HZA-863			HZA-714		HZA-829			HZA-091	
	FF/VI 100/25 mcg (n = 201)	FF 100 mcg (n = 205)	Placebo (n = 203)	FF/VI 200/25 mcg (n = 346)	FF/VI 100/25 mcg (n = 346)	FF 100 mcg (n = 347)	FF/VI 200/25 mcg (n = 155)	FP 500 mcg (n = 154)	FF/VI 200/25 mcg (n = 197)	FF 200 mcg (n = 194)	FP 500 mcg (n = 195)	FF/VI 100/25 mcg (n = 403)	FP/S 250/50 mcg (n = 403)
	(346.6)	(399.9)	(368.2)	(283.2)	(312.2)	(360.9)	(239.6)	(234.0)	(367.9)	(346.3)	(313.1)	(306.5)	(348.1)
Per cent, mean (SD)	28.0 (16.0)	30.7 (19.7)	27.5 (18.8)	27.0 (12.9)	29.0 (17.5)	31.1 (20.1)	27.3 (14.6)	27.0 (14.3)	29.6 (19.8)	29.2 (17.0)	29.6 (16.4)	26.4 (14.4)	29.0 (18.0)
FEV1 at Baseline													
N	201	205	203	344	342	342	155	154	191	193	194	401	401
Pre-bronchodilator, L (SD)	2.344 (0.642)	2.290 (0.617)	2.334 (0.626)	1.954 (0.582)	1.985 (0.556)	1.965 (0.598)	1.777 (0.493)	1.767 (0.552)	2.129 (0.654)	2.190 (0.676)	2.138 (0.673)	2.011 (0.639)	2.048 (0.625)
% predicted (SD)	70.6 (11.9)	70.5 (11.0)	70.2 (10.1)	62.1 (10.1)	62.6 (10.1)	61.1 (10.3)	67.51 (13.25)	67.55 (13.43)	66.6 (12.6)	66.7 (12.4)	67.6 (12.2)	68.0 (11.7)	68.8 (11.0)
Post-bronchodilator, L (SD)	NR			NR			NR		NR			NR	
Pre-study ICS Regimen, n (%)													
ICS alone	120 (60)	122 (60)	119 (59)	133 (38)	122 (35)	115 (33)	NR		47 (24)	44 (23)	49 (25)	125 (31)	123 (31)
ICS + LABA	81 (40)	83 (40)	84 (41)	213 (62)	224 (65)	232 (67)	NR		150 (76)	150 (77)	146 (75)	279 (69)	279 (69)

FEV_1 = forced expiratory volume in one second; FF = fluticasone furoate; FP = fluticasone propionate; ICS = inhaled corticosteroids; LABA = long-acting beta2-agonist; mcg = microgram; NR = not reported; S = salmeterol; SD = standard deviation; VI = vilanterol.

[a] FEV_1 reversibility at baseline is reported in only one study (HZA-863). Run-in periods are sufficiently short in each study that it is expected that screening and baseline values would be similar in value.

Source: Clinical Study Reports.[8-12]

TABLE 9: SUMMARY OF BASELINE CHARACTERISTICS — ASTHMA EXACERBATIONS

	HZA-837	
	FF/VI 100/25 mcg (n = 1,009)	FF 100 mcg (n = 1,010)
Age, mean years (SD)	41.1 (17.1)	42.3 (16.8)
Age, range	12 to 82	12 to 79
% patients ≥ 18 of age	858 (85.0)	880 (87.1)
Male, n (%)	348 (34)	321 (32)
Race		
White, n (%)	740 (73)	743 (74)
Asian, n (%)	112 (11)	110 (11)
Other, n (%)	157 (16)	157 (16)
Duration of asthma, mean years (SD)	15.3 (12.8)	15.8 (13.3)
Number of Exacerbations in the Past 12 Months (%)		
0	0	1 (< 1)
1	553 (55)	599 (59)
2	252 (25)	229 (23)
3	101 (10)	100 (10)
4	57 (6)	37 (4)
> 4	46 (5)	44 (4)
FEV_1 at Screening		
N	1,009	1,010
Pre-bronchodilator, L (SD)	2.144 (0.609)	2.101 (0.609)
% predicted (SD)	68.8 (10.6)	69.0 (10.4)
Post-bronchodilator, L (SD)	2.613 (0.736)	2.601 (0.751)
FEV_1 Reversibility at Screening[a]		
N	1,009	1,010
Absolute, mL (SD)	499.1 (265.4)	500 (260.3)
Per cent, mean (SD)	24.4 (12.7)	24.3 (12.1)
FEV_1 at Baseline		
N	1,009	1,010
Pre-bronchodilator, L (SD)	2.216 (0.643)	2.193 (0.640)
% predicted (SD)	72.0 (10.7)	71.9 (10.6)
Post-bronchodilator, L (SD)	NR	
Pre-study ICS Regimen, n (%)		
ICS alone	402 (40)	397 (39)
ICS/LABA	607 (60)	613 (61)

FEV_1 = forced expiratory volume in one second; FF= fluticasone furoate; ICS = inhaled corticosteroids; LABA = long-acting beta2-agonist; NR = not reported; SD = standard deviation; VI = vilanterol.

[a] FEV_1 reversibility at baseline was not reported. Run-in periods are sufficiently short that it is expected that screening and baseline values would be similar in value.

Source: Clinical Study Report.[13]

TABLE 10: SUMMARY OF BASELINE CHARACTERISTICS — SAFETY AND TOLERABILITY OUTCOMES ONLY

	HZA-839		
	FF/VI 200/25 mcg (n = 202)	FF/VI 100/25 mcg (n = 201)	FP 500 mcg (n = 100)
Age, mean years (SD)	38.5 (15.6)	39.7 (15.9)	38.6 (16.0)
Age, range	12 to 72	12 to 73	12 to 69
% patients ≥ 18 years of age	169 (83.7)	172 (85.6)	83 (83.0)
Male, n (%)	78 (39)	71 (35)	38 (38)
Race			
White, n (%)	134 (66)	135 (67)	68 (68)
Asian, n (%)	51 (25)	50 (25)	26 (26)
Other, n (%)	17 (8)	16 (8)	6 (6)
Duration of asthma, mean years (SD)	16.3 (12.8)	14.8 (11.3)	14.3 (13.0)
Number of Exacerbations in the Past 12 Months (%)			
0	140 (69)	139 (69)	74 (74)
1	41 (20)	43 (21)	21 (21)
2	15 (7)	15 (7)	4 (4)
3	4 (2)	2 (< 1)	0
4	1 (< 1)	1 (< 1)	0
> 4	1 (< 1)	1 (< 1)	1 (1)
FEV_1 at Screening			
N	202	201	100
Pre-bronchodilator, L (SD)	2.290 (0.655)	2.305 (0.661)	2.353 (0.672)
% predicted (SD)	74.1 (14.1)	74.2 (13.5)	75.2 (12.5)
Post- bronchodilator L (SD)	2.646 (0.621)	2.896 (0.845)	2.745 (0.715)
FEV_1 Reversibility at Screening[a]			
N	124	127	62
Absolute, mL (SD)	500.9 (249.1)	542.4 (316.6)	522.9 (278.1)
Per cent, mean (SD)	24.0 (12.2)	23.6 (14.1)	23.8 (11.3)
FEV_1 at Baseline			
N	202	201	100
Pre-bronchodilator, L (SD)	2.35 (0.70)	2.38 (0.68)	2.41 (0.70)
% predicted (SD)	75.8 (14.5)	76.7 (13.7)	76.7 (12.9)
Post-bronchodilator L (SD)	NR		
Pre-Study ICS Regimen, n (%)			
Any ICS medication	202 (100)	201 (100)	100 (100)

FEV_1 = forced expiratory volume in one second; FF= fluticasone furoate; ICS = inhaled corticosteroids; NR = not reported; SD = standard deviation; VI = vilanterol.

[a] FEV_1 reversibility at baseline was not reported. Run-in periods are sufficiently short that it is expected that screening and baseline values would be similar in value.

Source: Clinical Study Report.[14]

3.2.3 Interventions

Two studies (HZA-863 and HZA-839) evaluated both doses of FF/VI (100/25 mcg and 200/25 mcg) while the remaining trials evaluated a single dose of FF/VI: either 100/25 mcg (HZA-827, HZA-091, and HZA-837) or 200/25 mcg (HZA-714, HZA-829). The active comparators were all Health Canada–approved regimens: FF 100 mcg or 200 mcg once daily, FP 500 mcg twice daily, or FP/S 250/50 mcg twice daily (Table 11). The studies that assessed the two doses of FF/VI also incorporated an active comparator: FF 100 mcg in the case of study HZA-863 or FP 500 mcg in the case of study HZA-839. Study HZA-827, which evaluated FF/VI 100/25 mcg, was the only placebo-controlled trial that further included an active comparator, FF 100 mcg. At the moderate ICS/LABA dose, studies HZA-091 and HZA-837 compared FF/VI 100/25 mcg to FP/S 250/50 mcg and FF 100 mcg, respectively. At the higher ICS/LABA dose (i.e., FF/VI 200/25 mcg), the comparator was FP 500 mcg in study HZA-714; in study HZA-829, the comparators were FF 200 mcg and FP 500 mcg.

FF, as monotherapy or combination therapy, was delivered via the Ellipta dry powder inhaler, which was administered once daily in the evening. FP, either as monotherapy or combination therapy, was delivered via the Diskus/Accuhaler dry powder inhaler twice a day. During randomization, only patients in studies HZA-827 and HZA-863 were trained on the correct use of a placebo inhaler. Study HZA-827 specifically provided patients with up to three demonstrations on correct inhaler usage; and, if after the third attempt, the patient was still unable to use the inhaler correctly, patients were considered ineligible to enter the trial. This criterion was not reported in study HZA-863. In both studies, at weeks 2 and 4, patients' use of the inhaler was re-assessed and, if performed incorrectly, patients were given a demonstration on correct use of the inhaler. It is not clearly reported whether and how patients were trained on their inhaler in studies HZA-714, HZA-829, HZA-091, HZA-837, and HZA-839. The only studies in which the study medication was self-administered under supervision at each clinic visit were HZA091, HZA-837, and HZA-839.

Patients, investigators, and personnel involved in analyzing data remained blinded with regard to treatment assignment. A double-dummy design was employed in studies HZA-091, HZA-714, HZA-829, and HZA-839, where two different inhalers were required. Patients were given both the Ellipta and Diskus/Accuhaler devices and were instructed to administer one inhalation in the evening with the Ellipta device, and one inhalation in the morning and evening with the Diskus/Accuhaler device.

Patients meeting the screening eligibility criteria entered a run-in period of two to four weeks. Patients remained on their baseline ICS medication, but discontinued all other asthma-related medication. As noted, patients had to maintain a stable dose of their ICS for four weeks prior to visit 1 and throughout the run-in period. Upon randomization, treatment was replaced by the study medication. In all included trials, albuterol or salbutamol inhalation aerosol was permitted as rescue medication, although a 12-hour washout was required prior to performing pulmonary function tests. All other asthma medications were stopped at screening. Other prohibited medications included strong inhibitors of cytochrome P450 3A4, systemic corticosteroids, and any prescriptions or over-the-counter medication that could affect the course of asthma or interact with sympathomimetic amines. Non-asthmatic medications permitted during the study included intranasal corticosteroids; short-acting and long-acting antihistamines for the treatment of allergies; topical corticosteroids for dermatological diseases; and decongestants. All other medications for other disorders were permitted provided their use was not expected to affect lung function or safety.

TABLE 11: TREATMENT ARMS INCLUDED OR EXCLUDED FROM THE INCLUDED STUDIES

Study (Trial Duration)	FF/VI 100/ 25 mcg	FF/VI 200/ 25 mcg	FF 100 mcg	FF 200 mcg	FP 500 mcg	FP/S 250/ 50 mcg	Placebo
HZA-827 (12 weeks)	✓	×	✓	×	×	×	✓
HZA-863 (12 weeks)	✓	✓	✓	×	×	×	×
HZA-714 (12 weeks)	×	✓	×	×	✓	×	×
HZA-829 (24 weeks)	×	✓	×	✓	✓	×	×
HZA-091 (24 weeks)	✓	×	×	×	×	✓	×
HZA-837 (24 to 76 weeks)	✓	×	✓	×	×	×	×
HZA-839 (52 weeks)	✓	✓	×	×	✓	×	×

FF = fluticasone furoate; FP = fluticasone propionate; S = salmeterol; VI = vilanterol.
Source: Clinical Study Reports.[8-14]

3.2.4 Outcomes

See 0 for detailed information on the outcomes used in the included studies.

a) Asthma Exacerbations

Asthma exacerbation refers to episodes of more severe shortness of breath. In the trials, severe asthma exacerbation was defined according to the American Thoracic Society/European Respiratory Society taskforce guideline[30] as a deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspensions, or injection) for three days or more, or an in-patient hospitalization or emergency room visit due to asthma that required systemic corticosteroids. Time to first severe asthma exacerbation was the primary efficacy end point in study HZA-837. Exacerbation events were counted in which courses of corticosteroids separated by one week or more were considered to be separate exacerbation events. Specifically, in study HZA-837, patients were withdrawn if they experienced three severe asthma exacerbations in any six-month period or four severe asthma exacerbations during the double-blind treatment period. A review of the literature did not reveal any evidence on a minimal clinically important difference (MCID).

b) Quality of Life

The Asthma Quality of Life Questionnaire for 12 years and older (AQLQ +12) is a variant of the standardized version of the AQLQ. The questionnaire includes areas of quality of life (QoL) impairment that are important to adult asthmatic patients. The questions are grouped into four domains: activity limitations; symptoms; emotional function; and exposure to environmental stimuli, each scored against 7-point Likert scale (7 = not impaired at all; 1 = severely impaired).[31] The overall AQLQ score is the mean of all 32 items, and the individual domain scores are the means of the items within those domains.[31] Patients were asked to assess HRQoL, recalled from the previous two weeks. Although no MCID has been formally established for AQLQ +12, given its overlap with AQLQ, some consider the MCID for AQLQ to be appropriate (i.e., MCID = 0.5).[32-34]

The Asthma Control Test (ACT) is a five-item, patient-reported questionnaire to measure a patient's asthma control. Items captured include the impact of asthma on work, school, or home activities; shortness of breath; nocturnal awakening; use of rescue medication; and overall control.[35] Higher scores indicate better asthma control. An MCID of 3.0 has been established in the literature.[36]

c) Pulmonary Function

FEV_1 is the maximal volume of air after a full inspiration that can be forcibly exhaled in one second. It is measured electronically by spirometry. This measure can be converted to a percentage of predicted normal value that is adjusted by height, weight, and race. The percentage of predicted FEV_1 is a commonly reported pulmonary function test and is considered a valid marker for the degree of airway obstruction with asthma.[37] However, although it is widely used in clinical trials to evaluate the effectiveness of asthma treatments, there is little literature on the MCID for FEV_1-based measures. Historically, an MCID of 100 mL has been proposed, although little evidence exists to support this value.

Trough (pre-bronchodilator and pre-dose) FEV_1 was calculated as the highest of three technically acceptable FEV_1 measurements prior to study medication and any rescue medication usage. Lung-function measures were taken approximately 24 hours after a patient's last evening dose and at least six hours after any rescue medication usage. Mean change in trough FEV_1 compared with baseline was calculated as the co-primary efficacy end point in studies HZA-827 and HZA-829 at week 12 and week 24, respectively. Weighted mean serial FEV_1, over 0 hours to 24 hours post-dose, was calculated in a subset of patients in which serial FEV_1 was performed. Serial FEV_1 included pre-dose assessment within five minutes of administering the treatment, and post-dose assessments at 5 minutes, 15 minutes, and 30 minutes, and one, two, three, four, five, 12, 16, 20, 23, and 24 hours post-dose. Change in weighted 24-hour mean serial FEV_1 was the primary efficacy end point in studies HZA-863 and HZA-091 at week 12 and week 24, respectively, and the co-primary efficacy end point in HZA-827 and HZA-829, assessed at week 12 and week 24 respectively.

PEF is the peak volume expired, independent of time, during a forced exhalation.[38] PEF was taken twice daily using an electronic peak flow metre, once in the morning and once in the evening, and recorded at each time point by the patient in their eDiary. PEF was measured prior to study medication dose and any rescue medication. Mean change in daily evening PEF at week 12 was the primary end point in HZA-714. A search of the literature did not identify an MCID for PEF.

d) Use of Rescue Medication (e.g., Percentage of Rescue-free 24-hour Periods)

Patients were permitted to take albuterol or salbutamol inhalation aerosol as rescue medication for as-needed relief from their asthma symptoms. The use of rescue medication was recorded daily by patients in an electronic diary and reviewed by the investigator at each visit. A "rescue-free 24-hour period" related to the previous 24 hours in which patients did not require rescue medication. Change from baseline in the percentage of rescue-free 24-hour periods was calculated over the duration of the treatment period, with baseline defined as the last seven consecutive days prior to randomization. The manufacturer claimed that, by using an anchor-based approach, the MCID for change in the percentage of rescue-free 24-hour periods was between 7.7% and 14.7% in patients who were participating in the trials.

e) Daytime and Nighttime Asthma Symptom Scores (e.g., Per Cent of Symptom-free 24-hour Periods)

Symptom scores were recorded by patients in their eDiaries twice daily: at bedtime and upon rising, before taking any rescue or study medication and before PEF measurements. Patients rated their daytime and nighttime symptoms according to a 6-point or 5-point Likert scale, respectively (Table 12). Similarly, "symptom-free 24-hour period" related to the previous 24 hours in which patients did not have any asthma symptoms. To assess change from baseline, baseline was defined as the last seven consecutive days prior to randomization. Using an anchor-based approach, the manufacturer claimed

that the MCID for change in the percentage of 24-hour symptom-free periods was between 8.4% and 15.6% in the trials.

TABLE 12: DAYTIME AND NIGHTTIME ASTHMA SYMPTOM SCORE

Score	Description	
	Daytime Symptom	Nighttime Symptom
0	No symptoms during the day	No symptoms during the night
1	Symptoms for 1 short period during the day	Symptoms causing me to wake once (or wake early)
2	Symptoms for 2 or more short periods during the day	Symptoms causing me to wake twice or more (including waking early)
3	Symptoms for most of the day that did not affect my normal daily activities	Symptoms causing me to be awake for most of the night
4	Symptoms for most of the day that did affect my normal daily activities	Symptoms so severe that I did not sleep at all
5	Symptoms so severe that I could not go to work or perform normal daily activities	

Source: Clinical Study Reports.[8,9]

f) Adherence

Adherence was assessed in all trials by reviewing the dose counter on the inhaler(s). Adherence was calculated as a percentage of the expected number of doses to be administered in a given time.

g) Harms

AEs and serious adverse events (SAEs) were assessed in all studies from the baseline double-blind period to the end of follow-up. All AEs and SAEs were collected, documented, and reported to the sponsor by the study investigators. An AE was defined as an untoward medical occurrence in a patient temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. This could therefore include any exacerbation of a condition, emergence of a new condition, or signs (including abnormal laboratory findings), symptoms, or clinical sequelae of a suspected interaction or overdose of any treatment. This also included failures to produce expected benefits (such as lack of efficacy), abuse, or misuse. A treatment-emergent AE was defined as any event or worsening of an event that was related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or to a concomitant medication. An SAE could include any unexpected complication that resulted in death, was considered life-threatening, or resulted in disability or hospitalization.

3.2.5 Statistical Analysis

In all trials, the intention-to-treat (ITT) population was the primary population investigated in the efficacy analysis, with missing data handled by the last outcome carried forward (LOCF) approach. Analyses of the primary and secondary efficacy outcomes were repeated with the per-protocol (PP) population to assess the robustness of the study findings.

a) Determination of Sample Size

Studies HZA-827 and HZA-863 had a power of 83% and 94%, respectively, to detect treatment differences for both co-primary end points and the nominated powered secondary end point, assuming that 96 and 290 patients remained by the end of week 12 within each treatment group, respectively. Study HZA-829 was designed to have a statistical power of 92% to detect a treatment difference of

150 mL in pairwise comparisons on change from baseline in trough FEV_1 and 175 mL in weighted mean serial FEV_1 over 0 hours to 24 hours. Both studies HZA-091 and HZA-714 had a power of 90% in detecting a treatment difference in their primary efficacy outcomes (i.e., study HZA-091: 80 mL in weighted mean FEV_1; study HZA-714: 15 L/min in evening PEF values), assuming that 348 and 151 patients per treatment group were recruited with evaluable data, respectively.

Study HZA-837 was an event-driven study designed to have 90% power to detect a statistically significant treatment difference in the risk of experiencing a severe asthma exacerbation if a total of 1,000 patients were recruited. Sample size in the safety study, HZA-839, was determined based on feasibility rather than on statistical considerations; no formal sample size calculation was performed.

b) Statistical Test

Across the efficacy studies, statistical testing was conducted according to the nature of the outcome measure, with the hypothesis driven by a two-sided analysis at a 0.05 significance level. All efficacy analyses were adjusted for baseline scores for the particular efficacy measure, region, sex, and age groups, unless otherwise specified. No formal statistical hypothesis testing was performed for any of the safety end points.

Exacerbation: Time to first severe exacerbation was evaluated by Cox proportional hazards regression model to estimate the hazard ratio and 95% confidence interval (CI). Interactions between treatment and each covariate (e.g., baseline FEV_1, region, sex, and age) were investigated using Cox proportional hazards models. Cumulative incidence curves were derived using the Kaplan–Meier method.

AQLQ +12 and ACT: In the pulmonary function trials, AQLQ +12 and ACT were analyzed using an analysis of covariance (ANCOVA) model.

Lung Function: Evening trough FEV_1 and PEF values were analyzed using an ANCOVA model. In the subset of patients with a serial FEV_1 performed, the 24-hour serial FEV_1 included a pre-dose assessment (i.e., within five minutes of administering treatment) and post-dose assessments after five minutes, 15 minutes, and 30 minutes and one, two, three, four, five, 12, 16, 20, 23, and 24 hours. The weighted mean serial FEV_1 at 0 hours to 24 hours was calculated as the average area under the curve from the first non-missing time point to the last non-missing time point, and was analyzed using an ANCOVA model.

Rescue-Free or Symptom-Free 24-Hour Periods: If the data were normally distributed, this outcome would be analyzed statistically using an ANCOVA model. If the data were not normally distributed, the percentage of rescue- and symptom-free 24-hour periods would be categorized and analyzed by logistic regression. The adjusted mean percentage for each treatment and the estimated treatment difference for each comparison were further converted into an equivalent number of additional symptom- and rescue-free days per week by dividing the original value by 100, then multiplying by seven.

Resource Utilization: This outcome was summarized by standard descriptive statistics (e.g., mean, standard deviation).

c) Multiplicity

In the trials with efficacy analyses, a step-down, closed testing procedure was followed to account for multiplicity, with the hypothesis testing based on a two-sided, 5% significance level. The primary treatment comparison was required to be statistically significant for the primary end point in order to make inferences on the secondary end points, and a predefined hierarchy of the secondary end points was used. If a given statistical test failed to reject the null hypothesis of no treatment difference, then all tests lower down in the hierarchy were interpreted descriptively. If statistical significance was achieved at each level of hierarchy, then all other efficacy end points and defined pairwise treatment comparisons not included in the analysis hierarchy were tested without further multiplicity adjustment. The statistical testing strategy for each efficacy trial is highlighted in Table 12.

TABLE 13: MULTIPLICITY TESTS ACROSS EFFICACY STUDIES

	HZA-827[a]	HZA-863	HZA-714	HZA-829 [a]	HZA-091	HZA-837
Comparison at each end point	FF/VI vs. placebo FF/VI vs. FF FF vs. placebo	FF/VI vs. FF	FF/VI vs. FP	FF/VI vs. FF	FF/VI vs. FP/S	FF/VI vs. FF
Primary efficacy end point	1. Trough FEV_1; WM FEV_1	1. WM FEV_1	1. p.m. PEF	1. Trough FEV_1; WM FEV_1	1. WM FEV_1	1. Time to first severe asthma exacerbation
Secondary efficacy end point	2. Rescue-free 24-hour periods 3. Symptom-free 24-hour periods 4. AQLQ +12	2. Trough FEV_1 3. Rescue-free 24-hour periods 4. Symptom-free 24-hour periods 5. A.m. PEF 6. A.m. PEF	2. Rescue-free 24-hour periods 3. a.m. PEF 4. Symptom-free 24-hr periods 4. AQLQ +12	2. Rescue-free 24-hour periods 3. Symptom-free 24-hour periods 4. AQLQ +12		2. Rate of severe asthma exacerbation 3. Trough FEV_1

AQLQ +12 = Asthma Quality of Life Questionnaire for age 12 and up; FEV_1 = forced expiratory volume in one second; FF = fluticasone furoate; FP = fluticasone propionate; hr = hour; PEF = peak expiratory flow; VI = vilanterol; vs. = versus; WM = weighted mean.

[a] Both level 1 comparisons were required to be significant ($P = 0.05$) to progress to level 2, in which the testing of each end point depends on the significance achieved for all treatment comparisons of previous end points in the level 2 hierarchy.

Source: Clinical Study Reports.[8-13]

d) Missing Data

The statistical approach taken to handle missing data for the primary efficacy end points depended on the type of data measurement. Secondary end points, such as those relating to the daily dairy assessment, were calculated based on all available data, with no imputations performed on any missing data.

In the lung-function trials, missing FEV_1 data were imputed using the last observation carried forward (LOCF) approach. A sensitivity analysis on weighted mean change in FEV_1 was also conducted using a repeated measures mixed model. The weighted mean serial FEV_1 over 0 hours to 24 hours was calculated only if there was a non-missing measurement for the pre-dose (0-hour) time point and for at least one actual time point each between zero hours and five hours, between 15 hours and 21 hours, and between 21 hours and 25 hours. Otherwise, this end point was treated as missing. The area under the curve (AUC) was calculated from the pre-dose time point to the last non-missing time point; observations missing between two non-missing observations were handled by interpolation on the AUC.

In the long-term exacerbation study (HZA-837), patients who discontinued the trial without experiencing a severe asthma exacerbation were treated as censored. For study HZA-829, any missing data in the analysis were treated as missing.

e) Subgroup Analyses

The lung-function trials (HZA-827, HZA-863, HZA-714, HZA-829, and HZA-091) did not define a priori subgroups. In contrast, the long-term asthma exacerbation study HZA-837 defined a priori and examined two subgroups: race and country.

f) Analysis Populations

In the trial program, several analysis populations were defined.

The total population comprised all patients screened who had a record in the study database. This population was used to tabulate the reasons for withdrawal before randomization.

The ITT population comprised all patients randomized to treatment who received at least one dose of the study medication. This constituted the primary population for all analyses of efficacy and safety measures (excluding urinary cortisol analyses).

The PP population comprised all patients in the ITT population who did not have any full protocol deviations. Protocol deviations may be full or partial. Patients with only partial deviations were considered part of the PP population, but from the date of their deviation onward, their data were excluded. The decision to exclude a patient or part of their data from the PP population was made prior to breaking the study's blind. This population was used only for confirmatory analysis of the primary efficacy end point(s) and for some of the pre-specified, powered secondary efficacy end points. In some cases, post-hoc analyses were conducted to exclude entire sites due to protocol deviation. Studies HZA-827 and HZA-829 removed 61 patients (10%) from two investigators and 48 patients (8.2%) from one investigator, respectively. For similar concerns, studies HZA-837 and HZA-091 removed 33 (1.6%) and 57 (7.1%) patients from two investigator sites.

3.3 Patient Disposition

Patient disposition is summarized in Table 14, Table 15, and Table 16. Study completion was not consistent across trials, and varied by treatment groups within each study. A greater proportion of patients discontinued treatment following randomization in study HZA-839 (range: 19.9% to 29.0%) compared with the other studies (range: 7.2% to 25.6%). This is likely due to the longer study duration (52 weeks). Differential dropout was observed in several of the trials; in general, higher discontinuation rates were found in the placebo and monotherapy treatment groups than in the combination treatment group. The most common reason for study discontinuation was lack of efficacy, followed by withdrawal of consent.

3.4 Exposure to Study Treatments

Exposure to study treatment was calculated as the number of days patients were participating in the trial. Overall, the median exposure to study treatment was similar between studies, and was close to the full duration of the respective studies: 12 weeks in HZA-827, HZA-863, and HZA-714; 24 weeks in HZA-829 and HZA-091; and 52 weeks in HZA-839 (Table 17).

Overall, across all trials, it was observed that the number of days patients were exposed to treatment was highest for patients on combination therapy. Patients who were treated with monotherapy had higher rates of short exposure, concordant with the observation of premature withdrawals in the monotherapy treatment groups (Table 14, Table 15, and Table 16).

TABLE 14: PATIENT DISPOSITION — LUNG-FUNCTION PROFILE

	HZA-827			HZA-863			HZA-714		HZA-829			HZA-091	
	FF/VI 100/25 mcg	FF 100 mcg	Placebo	FF/VI 200/25 mcg	FF/VI 100/25 mcg	FF 100 mcg	FF/VI 200/25 mcg	FP 500 mcg	FF/VI 200/25 mcg	FF 200 mcg	FP 500 mcg	FF/VI 100/25 mcg	FP/S 250/ 50 mcg
Screened, N	1,110			2,019			539		1,206			1,564	
Screen failure, N (%)	379 (34)			523 (26)			151 (28)		478 (40)			623 (40)	
Run-in, N (%)	731 (66)			1,496 (74)			388 (72)		728 (60)			941 (60)	
Run-in failure, N (%)	120 (11)			456 (23)			75 (14)		141 (12)			135 (9)	
Randomized, N	202	205	203	346	346	347	157[b]	156[b]	197	194	196[c]	403	403
Discontinued, N (%)	22 (10.9)	20 (9.8)	52 (25.6)	25 (7.2)	32 (9.2)	51 (14.7)	19 (12.3)	35 (22.7)	28 (14.2)	48 (24.7)	34 (17.4)	45 (11.2)	46 (11.4)
Lack of efficacy	7 (3.5)	6 (2.9)	32 (15.8)	11 (3.2)	13 (3.8)	33 (9.5)	12 (7.7)	26 (16.9)	6 (3.0)	21 (10.8)	18 (9.2)	20 (5.0)	11 (2.7)
Withdrew consent	3 (1.5)	6 (2.9)	6 (3.0)	5 (1.4)	8 (2.3)	8 (2.3)	2 (1.3)	3 (1.9)	4 (2.0)	13 (6.7)	7 (3.6)	7 (1.7)	9 (2.2)
Investigator discretion	6 (3.0)	7 (3.4)	6 (3.0)	4 (1.2)	4 (1.2)	3 (< 1)	2 (1.3)	0	8 (4.1)	4 (2.1)	1 (< 1)	0	1 (< 1)
Lost to follow-up	2 (< 1)	1 (< 1)	0	1 (< 1)	1 (< 1)	0	1 (< 1)	0	0	2 (1.0)	1 (< 1)	5 (1.2)	7 (1.7)
AE	2 (< 1)	0	1 (< 1)	3 (< 1)	3 (< 1)	4 (1.2)	2 (1.3)	2 (1.3)	7 (3.6)	3 (1.5)	2 (1.0)	6 (1.5)	8 (2.0)
Protocol deviation	2 (< 1)	0	7 (3.4)	0	3 (< 1)	2 (< 1)	0	4 (2.6)	3 (1.5)	5 (2.6)	5 (2.6)	7 (1.7)	10 (2.5)
Other	0	0	0	1 (< 1)	0	1 (< 1)	0	0	0	0	0	0	0
ITT, N (%[d])	201[a] (> 99)	205 (100)	203 (100)	346 (100)	346 (100)	347 (100)	155 (99)	154 (99)	197 (100)	194 (100)	195[c] (> 99)	403 (100)	403 (100)
PP, N (%[d])	181 (90)	184 (90)	181 (89)	324 (94)	327 (95)	329 (95)	122 (78)	118 (76)	172 (87)	175 (90)	168 (86)	361 (90)	380 (94)
Urinary Cortisol, N (%[d])	153 (76)	156 (76)	136 (67)	NA			NA		140 (71)	126 (65)	123 (63)	103 (26)	106 (26)

AE = adverse event; FF = fluticasone furoate; FP = fluticasone propionate; ITT = intention-to-treat; NA = not applicable; PP = per-protocol; S = salmeterol; VI = vilanterol.

[a] One patient was not randomized, but received FF 100 mcg in error. The patient was removed from the ITT population.

[b] Four patients were randomized in error and did not receive any study medication. These patients were removed from the ITT population.

[c] One patient was randomized in error and did not receive the study drug. The patient was removed from the ITT population.

[d] The denominator is the number of patients randomized.

Source : Clinical Study Reports.[8-12]

TABLE 15: PATIENT DISPOSITION — ASTHMA EXACERBATION

	HZA-837	
	FF/VI 100/25 mcg	FF 100 mcg
Screened, N	2,668	
Screen failure, N (%)	485 (18)	
Run-in, N (%)	2,183 (82)	
Run-in failure, N (%)	162 (6)	
Randomized, N	1,009	1,011
Discontinued, N (%)	124 (12.3)	147 (14.6)
Lack of efficacy	13 (1.3)	22 (2.2)
Withdrew consent	55 (5.5)	53 (5.2)
Investigator discretion	6 (< 1)	9 (< 1)
Lost to follow-up	9 (< 1)	11 (1.1)
AE	15 (1.5)	19 (1.9)
Protocol deviation	17 (1.7)	26 (2.5)
Other	9 (< 1)	7 (< 1)
ITT, N (%[b])	1,009 (100)	1,010 (> 99)[a]
PP, N (%[b])	889 (88)	903 (89)
Urinary cortisol, N (%[b])	NA	

AE = adverse event; FF = fluticasone furoate; ITT = intention-to-treat; NA = not applicable; PP = per-protocol; VI = vilanterol.
[a] One patient was randomized, but did not receive the study drug.
[b] The denominator is the number of patients randomized.
Source: Clinical Study Report.[13]

TABLE 16: PATIENT DISPOSITION — SAFETY AND TOLERABILITY OUTCOMES ONLY

	HZA-839		
	FF/VI 200/25 mcg	FF/VI 100/25 mcg	FP 500 mcg
Screened, N	708		
Screen failure, N (%)	91 (13)		
Run-in, N (%)	617 (87)		
Run-in failure, N (%)	114 (16)		
Randomized, N	202	201	100
Discontinued, N (%)	41 (20.3)	40 (19.9)	29 (29.0)
Lack of efficacy	4 (2.0)	1 (< 1)	1 (1.0)
Withdrew consent	7 (3.5)	10 (5.0)	9 (9.0)
Investigator discretion	0	1 (< 1)	3 (3.0)
Lost to follow-up	3 (1.5)	1 (< 1)	4 (4.0)
AE	3 (1.5)	5 (2.5)	6 (6.0)
Protocol deviation	8 (4.0)	8 (4.0)	2 (2.0)
Other	16 (7.9)	14 (7.0)	4 (4.0)
ITT, N (%[b])	202 (100)	201 (100)	100 (100)
PP, N (%[b])	NA		
Urinary cortisol, N (%[b])	143 (71)	143 (71)	76 (76)

AE = adverse event; FF = fluticasone furoate; FP = fluticasone propionate; ITT = intention-to-treat; NA = not applicable; PP = per-protocol; VI = vilanterol.
[a] The prednisolone 10 mg arm is not presented.
[b] The denominator is the number of patients randomized.
Source: Clinical Study Report.[14]

TABLE 17: SUMMARY OF EXPOSURE

Study and Treatment Group (Trial Duration)	Inhaler	Exposure (Days)[a]			Range of Exposure (Days), n (%)						
		N	Mean (SD)	Median (Min, Max)	≤ 28	29 to 56	57 to 84	85 to 112	113 to 140	141 to 168	≥ 169
HZA-827 (12 weeks)											
FF/VI 100/25 mcg	NDPI	201	80.8 (13.0)	85 (13, 91)	4 (2)	8 (4)	73 (36)	116 (58)			
FF 100 mcg	NDPI	205	80.6 (14.2)	85 (4, 91)	6 (3)	7 (3)	77 (38)	115 (56)			
Placebo	NDPI	203	71.7 (25.1)	84 (3, 98)	30 (15)	9 (4)	74 (37)	88 (44)			
HZA-863 (12 weeks)											
FF/VI 200/25 mcg	NDPI	346	81.2 (13.2)	84 (7, 92)	12 (3)	4 (1)	166 (48)	164 (47)			
FF/VI 100/25 mcg	NDPI	346	79.6 (16.7)	84 (1, 93)	18 (5)	8 (2)	161 (47)	159 (46)			
FF 100 mcg	NDPI	347	77.7 (18.9)	84 (1, 109)	22 (6)	12 (3)	170 (49)	143 (41)			
HZA-714 (12 weeks)											
FF/VI 200/25 mcg	NDPI Diskus	154 154	80.3 (12.0) 80.3 (12.0)	84 (27, 90) 84 (27, 90)	28 (1) 2 (1)	7 (5) 7 (5)	116 (75) 116 (75)	29 (19) 29 (19)			
FP 500 mcg	NDPI Diskus	154 154	74.2 (20.9) 74.2 (20.9)	84 (2, 88) 84 (2, 88)	14 (9) 14 (9)	13 (8) 12 (8)	93 (60) 93 (60)	34 (22) 35 (23)			
HZA-829 (24 weeks)											
FF/VI 200/25 mcg	NDPI Diskus	196 196	156.7 (34.8) 157.2 (34.8)	168 (7, 188) 169 (9, 189)	7 (4) 7 (4)	28 (1) 2 (1)	28 (1) 2 (1)	9 (5) 9 (5)	28 (2) 3(2)	86 (44) 74 (38)	87 (44) 99 (51)
FF 200 mcg	NDPI Diskus	191 191	144.7 (49.3) 145.1 (49.3)	168 (3, 188) 168 (3, 189)	16 (8) 13 (7)	6 (3) 8 (4)	28 (2) 5 (3)	8 (4) 8 (4)	7 (4) 3(2)	75 (39) 71 (37)	75 (39) 83 (43)
FP 500 mcg	NDPI Diskus	195 195	149.4 (46.9) 150.0 (46.8)	168 (2, 199) 169 (3, 200)	15 (8) 14 (7)	6 (3) 5 (3)	28 (3) 7 (4)	28 (2) 3 (2)	1 (< 1) 0	81 (42) 67 (34)	84 (43) 99 (51)
HZA-091 (24 weeks)											
FF/VI 100/25 mcg	NDPI Diskus	403 403	160.0 (30.2) 161.0 (30.3)	NR (1, 224) NR (1, 224)	(2) 6 (1)	8 (2) 7 (2)	8 (2) 10 (2)	28 (< 1) (< 1)	28 ((1) 5 (1)	372 (92) 372 (92)	
FP/S 250/50 mcg	NDPI Diskus	403 403	158.4 (32.8) 159.2 (33.1)	NR (1, 185) NR (1, 186)	10 (2) 8 (2)	10 (2) 11 (3)	28 (< 1) 5 (1)	7 (2) 6 (1)	7 (2) 7 (2)	365 (90) 366 (91)	

Study and Treatment Group (trial duration)	Inhaler	Exposure (Days)			Range of Exposure (Weeks), n (%)						
		N	Mean (SD)	Median (min, max)	≤ 13	13 to 26	26 to 39	39 to 52	52 to 65	65 to 78	≥ 78
HZA-837 (24 weeks to 76 weeks)											
FF/VI 100/25 mcg	NDPI	1009	369.3 (92.2)	369 (1, 543)	42 (4)	15 (1)	30 (3)	371 (37)	409 (41)	142 (14)	0
FF 100 mcg	NDPI	1010	363.7 (100.4)	366 (1, 539)	48 (5)	32 (3)	31 (3)	362 (36)	397 (39)	140 (14)	0
HZA-839 (52 weeks)											
FF/VI 200/25 mcg	NDPI Diskus	202	326.1 (98.4) 326 (98.4)	364 (1, 386) 364 (1, 386)	14 (7) 14 (7)	28 (2) 5 (2)	10 (5) 10 (5)	80 (40) 73 (36)	93 (46) 100 (50)		
FF/VI 100/25 mcg	NDPI Diskus	201	327.9 (95.5) (93.5)	364 (1, 402) 364 (1, 402)	15 (7) 15 (7)	28 (< 1) 2 (< 1)	14 (7) 14 (7)	82 (41) 75 (37)	88 (44) 95 (47)		
FP 500 mcg	NDPI Diskus	100	301.5 (112.5) 301.6 (112.6)	363.5 (19, 384) 364 (19, 384)	11 (11) 10 (10)	7 (7) 8 (8)	8 (8) 8 (8)	31 (31) 31 (31)	43 (43) 43 (43)		

FF= fluticasone furoate; FP = fluticasone propionate; NDPI = novel dry powder inhaler; NR = not reported; S = salmeterol; SD = standard deviation; VI = vilanterol.
[a] Exposure calculated as: (date treatment stopped – date treatment started) + 1.
Source: Clinical Study Reports.[8-14]

3.5 Critical Appraisal

3.5.1 Internal Validity

a) Selection, Allocation, and Disposition of Patients

In the included studies, patient characteristics were generally well balanced between treatment groups. Up to 25% of patients in the included studies had one or more protocol deviations. Only patients classified with a full protocol deviation (i.e., entrance criteria deviation, prohibited medication, non-compliance, pregnancy) were excluded from the PP efficacy dataset. In some cases, this represented 12% of all patients participating in the trial. As the overall proportion of patients with major protocol violations appeared to be similar between treatment groups, this may not have had a significant impact on the efficacy evaluation. For most circumstances, reanalysis of the primary and secondary outcomes on the PP population (i.e., in studies HZA-827, HZA-863, HZA-714, HZA-829, HZA-091, and HZA-837) led to results that were broadly similar to the ITT analysis.

There was an equal distribution between treatment groups in the number of patients who were using ICS alone and the number using an ICS/LABA combination inhaler before study entry. However, it was not reported whether the mean ICS dose before study entry was similar between the treatment groups. Consequently, a certain proportion of patients would have received an increase in ICS dose after randomization, whereas others would have received a similar dose to that prior to randomization. The clinical expert involved in the review did not expect that this would have a measurable impact on the validity of the findings, because response is likely more dependent on baseline FEV_1 and its reversibility (except for exacerbations, which will depend on the frequency of previous exacerbations in the preceding year).

All included studies were double-blind — and, if necessary, double-dummy — in design to preserve blinding to treatment allocation. However, in studies that compared combination and monotherapy treatments, rates of discontinuation and withdrawal due to lack of efficacy were higher in patients in the monotherapy group. Indeed, treatment exposure was shorter in the monotherapy arms than in the combination therapy arms, potentially suggesting that blinding may have been broken in the monotherapy groups, as patients might have been aware that they were not on the study drug. An imbalanced discontinuation rate, with a higher rate of patients discontinuing due to a lack of efficacy in the monotherapy arms, along with the use of LOCF to handle missing data, may have introduced bias against the combination therapy arms that would have underestimated the treatment effect, though the magnitude of the potential bias is unknown. Attrition rates in the long-term safety study were also high within each treatment group, ranging from 19.9% to 29.0%.

b) Study Design Features

In several of the studies, treatment adherence was not well established. Some trials measured adherence based on inhaler dose counters. Count measures are a poor proxy, as they measure the number of times an inhaler has been applied and do not count the number of times the device was *correctly* applied (i.e., proper inhalation of the desired dose). One way to assess adherence with inhaler therapy more accurately is to have an observer watch the patient deliver a dose to themselves and provide commentary and suggestions for improvement. The issue of administration was addressed by the inhaler use assessment in two studies: HZA-827 and HZA-863. It appears that the majority of patients (> 99%) were using their inhalers correctly at subsequent visits. However, in several of the trials, it remained unclear whether patients were adequately trained on the use of the inhalers, as details of training on the inhaler and an assessment of inhaler use were not reported (i.e., HZA-714, HZA-829, HZA-091, and HZA-837). Therefore, it remains unknown to what extent the study patients in

both treatment groups correctly administered their inhalers on a daily basis in the above-listed trials. However, as this concern applies to all treatment groups, issues of adherence would likely have affected the reliability of the estimates rather than their validity.

The included studies provided no information on quality assessment of lung-function measurements using spirometry. It remains uncertain whether invalid spirometric measurements could have had an impact on the efficacy assessments; however, bias due to such invalid measurements is perhaps minimal because there is little reason to believe they would have occurred preferentially in one treatment group compared with another.

A strong placebo effect was observed in the placebo-controlled trial, study HZA-827. For instance, over the course of 12 weeks of placebo treatment, patients reported a 222 mL improvement in evening trough FEV_1 and a 212 mL improvement in weighted mean FEV_1 compared with baseline values. The placebo response was apparent across all outcomes studied in this trial. This may have compromised the evaluation of the comparative efficacy of FF/VI.

c) Statistical Analyses

The efficacy studies were designed to show superiority between FF/VI and comparator arms (i.e., monotherapies and/or combination therapies). The primary approach to data analysis, according to the Clinical Study Report, was the ITT population. Although standard ITT is considered a conservative approach in research questions that are framed for superiority, the method of analysis in these trials was not a true ITT. ITT analyzes all patients who are randomly assigned to one treatment together, regardless of whether they had completed or even received the treatment. In the included trials, only patients who had received at least one study dose were included in the ITT population. However, the magnitude of the impact of potential bias resulting from this is likely minimal, because in most cases, the study-defined ITT population numbers were very similar to the numbers randomized.

Except for the long-term safety study, all trials appeared to be adequately powered to detect differences in their primary end points and, in some cases, in their secondary end points. However, it remains unclear whether the majority of secondary outcomes presented in this report (e.g., AQLQ +12, ACT, symptom-free 24-hour period, health care resource consumption) were adequately powered.

By using a hierarchical approach, multiplicity was adjusted for secondary outcomes including AQLQ +12, evening trough PEF, etc.; however, for study HZA-829 (24 weeks), a multiple pair of comparisons between FF 200/25 mcg versus FF 200 mcg or FP 500 mcg, respectively, on evening trough FEV_1 ($P < 0.001$) may have suffered from an inflated type I error rate, since no adjustment for multiplicity was performed.

All identified trials recruited patients ≥ 12 years of age. In the majority of the trials, the proportion of adolescents was less than 10% of the complete study population, with the exception of studies HZA-827, HZA-837, and HZA-839 (overall percentage of patients < 18 years of age: 13.5%, 14%, and 16%, respectively). In studies HZA-827 and HZA-839, the extent to which the efficacy and safety outcomes were affected by the higher proportion of younger patients is unknown. Although study HZA-837 did conduct a subgroup analysis on various adult subgroup populations, its interpretation is limited, as it is a post-hoc analysis and can only be considered exploratory in nature. Beyond study HZA-837, no subgroup analysis by age was defined a priori and conducted.

3.5.2 External Validity

According to the clinical expert consulted as part of this review, the demographics of the recruited patients in all seven trials were comparable to patients who would be candidates for combination therapy in Canadian medical practices. Individuals recruited in these studies were patients with asthma on a prior stable dose of ICS alone or ICS ± LABA treatment, with reversibility of $FEV_1 \geq 12\%$ and ≥ 200 mL and pre-bronchodilator FEV_1 40% or 50% to 90% of predicted normal. Of note, participants enrolled in the studies had to have been taking a stable dose of ICS (FP 200 mcg or more) before study entry. As well, in all but study HZA-827, more than 60% of the populations were already taking an ICS/LABA combination inhaler. Therefore, extrapolating the results of the studies to patients whose asthma is inadequately controlled on low-dose ICS alone may not be appropriate. The clinical expert involved in the review expressed concerns about the potentially inappropriate prescribing of FF/VI to patients with mild asthma, especially by caregivers who are not respirologists.

Overall, the majority of trials had short durations: 12 weeks to 24 weeks, with one safety study lasting 52 weeks and one exacerbation-driven study having an average treatment exposure of 52 weeks. As such, long-term efficacy and safety are uncertain for a medication that would be routinely used chronically in asthma maintenance treatment.

Although the trial was designed to recruit patients with asthma aged 12 years or older, the Health Canada–approved indication was restricted to adult patients aged 18 years or older, as clinical benefits could not be established clearly in this specific age subgroup, and long-standing safety concerns remain with the use of LABAs.[27] Therefore, challenges remain in interpreting the study findings, as all reports were for the total population and were aggregated to include both adult and adolescent patients.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported in Section 2.2, Table 4.

3.6.1 Asthma Exacerbations

All trials reported on the incidence of severe asthma exacerbations within the entire population, including adolescents (12 to 18 years of age). Across most lung-function studies, the incidence of severe asthma exacerbation was low (Table 19). Even among the placebo arm of one trial, only 4% of total patients on placebo experienced a severe asthma exacerbation. In these studies, no obvious trends or differences were observed between treatment groups and no between-treatment statistical comparisons were conducted.

In study HZA-837, which was designed to evaluate exacerbation rates and had recruited patients with a likely higher baseline risk of experiencing an asthma exacerbation, the rate of severe asthma exacerbations per patient per year was 0.19 in the FF 100 mcg once-daily group (approximately one every five years) and 0.14 in the FF/VI 100/25 mcg once-daily group (approximately one every seven years). This represented a 25% reduction in the rate of severe exacerbation in patients treated with FF/VI compared with FF. With respect to time to first severe asthma exacerbation, the hazard ratio for FF/VI versus FF was 0.795 (95% CI, 0.642 to 0.985; $P = 0.036$) at 52 weeks. This represents a nearly 20% relative reduction in risk of first severe asthma exacerbation in patients treated with FF/VI 100/25 mcg compared with FF 100 mcg.

TABLE 18: INCIDENCE OF SEVERE EXACERBATIONS OF ASTHMA — ASTHMA EXACERBATION STUDY

	HZA-837	
	FF/VI 100/25 mcg	FF 100 mcg
N	1,009	1,010
Adjusted probability of 1 + severe asthma exacerbation (95% CI)[a]	12.8 (10.7 to 14.9)	15.9 (13.5 to 18.2)
Time to first severe asthma exacerbation, adjusted HR	0.795 (0.642 to 0.985)	
Rate of severe asthma exacerbation per patient per year	0.14	0.19
Total number of severe exacerbations	186	256
Number of severe exacerbations per patient (%)		
0	855 (85)	824 (82)
1	119 (12)	125 (12)
2	25 (2)	40 (4)
3	9 (< 1)	19 (2)
4	1 (< 1)	1 (< 1)
5	0	1 (< 1)

CI = confidence interval; FF = fluticasone furoate; HR = hazard ratio; VI = vilanterol.
[a] Cox proportional Hazard model estimate at mean baseline FEV_1, age, and proportional coefficients for sex and region.
Source: Clinical Study Report.[13]

3.6.2 Quality of Life

QoL was measured within the lung-function studies and presented as an aggregate of the entire study population (i.e., adolescents and adults).

All treatment groups had similar baseline AQLQ +12 total scores. By the end of the double-blind treatment period, the AQLQ +12 score had improved in all groups and, similarly, the largest relative gains were observed in patients who were on combination therapy. In most cases, the difference in change in QoL between treatments, at both weeks 12 and 24, could not be compared statistically, as hierarchical testing was stopped before this outcome. The only appropriate statistical tests as per the pre-specified analysis plan were done in studies HZA-863 and HZA-829, in which no statistically significant improvement in QoL emerged between the different treatment groups.

In terms of ACT, the baseline values were similar across treatment groups within each study (Table 21). The highest baseline ACT scores were observed in study HZA-091 (18.9 in FF/VI 100/25 mcg once daily and 18.8 in FP/S mcg twice daily), which is expected given that patients had a longer history of asthma and that a greater number of these patients were on an ICS/LABA combination treatment prior to study enrolment. By the end of the treatment period, ACT scores had improved in all treatment groups. With the exception of study HZA-091, which compared combination therapies, and the placebo arm of HZA-827, this improvement from baseline was clinically significant in the other studies, with scores improving by more than 3.0 points. As in the AQLQ +12, the largest relative gains were noted in patients who were receiving combination therapy. As per the pre-specified analysis plan, only statistical testing was appropriate in study HZA-863. Patients on FF/VI 100/25 mcg once daily reported a statistically significantly greater improvement in ACT than did patients on FF 100 mcg once daily (least squares [LS] mean change 0.9; 95% CI, 0.3 to 1.5; *P* = 0.002), although this difference is unlikely to be clinically meaningful.

TABLE 19: INCIDENCE OF SEVERE EXACERBATIONS OF ASTHMA IN THE ENTIRE STUDY POPULATION (INTENTION-TO-TREAT)

	HZA-827			HZA-863			HZA-714		HZA-829			HZA-091		HZA-837		HZA-839		
	FF/VI 100/ 25 mcg	FF 100 mcg	Placebo	FF/VI 200/ 25 mcg	FF/VI 100/ 25 mcg	FF 100 mcg	FF/VI 200/ 25 mcg	FP 500 mcg	FF/VI 200/ 25 mcg	FF 200 mcg	FP 500 mcg	FF/VI 100/ 25 mcg	FP/S 250/ 25 mcg	FF/VI 100/ 25 mcg	FF 100 mcg	FF/VI 200/ 25 mcg	FF/VI 100/ 25 mcg	FP 500 mcg
N	201	205	203	346	346	347	155	154	197	194	195	403	403	1,009	1,010	202	201	100
Severe exacerbations (%)	1 (< 1)	4 (2)	9 (4)	4 (1)	3 (< 1)	7 (2)	1 (< 1)	3 (2)	0	6 (3)	2 (1)	10 (2)	12 (3)	186 (18)	256 (25)	6 (3)	3 (1)	3 (3)
Difference: FF/VI vs. placebo	NR			NR			NR		NR			NR		NR		NR		
Difference: FF/VI vs. monotherapy																		
Difference: FF/VI vs. combination therapy																		

FF = fluticasone furoate; FP = fluticasone propionate; NR = not reported; S = salmeterol; VI = vilanterol; vs. = versus.
Note: Manufacturer reported severe exacerbation as part of safety outcomes.
Source: Clinical Study Reports.[8-14]

TABLE 20: RESULTS OF AQLQ +12 TOTAL SCORE IN THE ENTIRE STUDY POPULATION (INTENTION-TO-TREAT)

	HZA-827			HZA-863			HZA-714		HZA-829			HZA-091	
	FF/VI 100/25 mcg	FF 100 mcg	Placebo	FF/VI 200/25 mcg	FF/VI 100/25 mcg	FF 100 mcg	FF/VI 200/25 mcg	FP 500 mcg	FF/VI 200/25 mcg	FF 200 mcg	FP 500 mcg	FF/VI 100/25 mcg	FP/S 250/25 mcg
Total, N	201	201	201	346	345	347	155	154	195	190	193	394	396
Baseline mean (SD)	4.78 (1.00)	4.69 (0.89)	4.78 (1.03)	4.52 (1.07)	4.46 (1.08)	4.50 (1.04)	4.53 (0.93)	4.52 (0.90)	4.37 (0.92)	4.50 (1.00)	4.45 (1.05)	5.35 (1.13)	5.37 (1.13)
End of double-blind period,[a] N	180	186	151	326	318	300	140	123	169	144	158	348	341
End of double-blind period mean (SD)	5.69 (0.89)	5.46 (0.88)	5.39 (0.85)	5.50 (1.05)	5.32 (1.07)	5.31 (1.06)	5.34 (0.93)	5.22 (1.00)	5.35 (1.04)	5.38 (1.13)	5.35 (1.09)	5.85 (1.02)	5.79 (1.01)
Change from baseline, mean (SD)	0.85 (0.92)	0.79 (0.91)	0.64 (0.85)	0.97 (1.09)	0.86 (1.08)	0.74 (1.05)	0.80 (0.93)	0.69 (0.90)	0.93 (0.89)	0.92 (0.87)	0.85 (1.03)	0.47 (0.94)	0.36 (0.90)
LS mean change,[a] (SE)	0.91 (0.06)	0.76 (0.06)	0.61 (0.06)	0.97 (0.05)	0.84 (0.05)	0.76 (0.05)	0.80 (0.07)	0.69 (0.07)	0.93 (0.07)	0.88 (0.07)	0.90 (0.07)	0.46 (0.04)	0.37 (0.04)
Difference: vs. placebo (95% CI), *P* value	**0.30 (0.13 to 0.46), *P* < 0.001**	0.15 (–0.01 to 0.31), *P* = 0.073											
Difference: FF/VI vs. monotherapy (95% CI), *P* value	0.15 (–0.01 to 0.30)[b]			NR	0.08 (–0.07 to 0.22), *P* = 0.303		0.12 (–0.08 to 0.32)[b]		FF: 0.05 (–0.14 to 0.24), *P* = 0.587 FP: 0.03 (–0.16 to 0.21)[b]				
Difference: FF/VI vs. combination therapy (95% CI), *P* value				0.14 (–0.01 to 0.28)[c]	NR							0.09 (–0.03 to 0.21)[b]	

AQLQ +12 = Asthma Quality of Life Questionnaire for 12 years and older; CI = confidence interval; FF = fluticasone furoate; FP = fluticasone propionate; LS = least squares; NR = not reported; S = salmeterol; SD = standard deviation; SE = standard error; VI = vilanterol; vs. = versus.

[a] ANCOVA model with covariates of baseline value, region, sex, age, and treatment group.

[b] Because of the hierarchical testing procedure to account for multiplicity, statistical significance cannot be concluded in this comparison.

[c] Statistical testing was not done for the comparison of FF/VI 200/25 mcg versus FF/VI 100/25 mcg.

Source: Clinical Study Reports.[8-12]

TABLE 21: RESULTS OF ASTHMA CONTROL TEST IN THE ENTIRE STUDY POPULATION (INTENTION-TO-TREAT)

	HZA-827			HZA-863			HZA-714		HZA-829			HZA-091	
	FF/VI 100/25 mcg	FF 100 mcg	Placebo	FF/VI 200/25 mcg	FF/VI 100/25 mcg	FF 100 mcg	FF/VI 200/25 mcg	FP 500 mcg	FF/VI 200/25 mcg	FF 200 mcg	FP 500 mcg	FF/VI 100/25 mcg	FP/S 250/25 mcg
Total, N	201	205	203	346	346	347	155	154	197	194	195	400	400
Baseline mean (SD)	15.8 (3.5)	15.5 (3.3)	15.5 (3.6)	14.2 (3.6)	14.0 (3.6)	14.4 (3.5)	15.3 (3.8)	15.0 (3.6)	13.5 (3.2)	14.1 (3.5)	14.0 (3.6)	18.9 (4.1)	18.8 (4.3)
End of double-blind period,[a] N	185	189	154	326	318	300	140	123	170	147	162	356	351
End of double-blind period mean (SD)	20.2 (3.4)	19.4 (3.3)	18.4 (3.5)	19.5 (4.2)	18.8 (3.9)	18.1 (3.9)	20.0 (3.9)	19.5 (3.6)	19.3 (3.9)	19.3 (4.0)	18.6 (4.2)	21.2 (3.5)	20.9 (3.7)
Change from baseline, mean (SD)	4.3 (4.2)	3.9 (3.8)	2.5 (3.8)	5.4 (4.7)	4.9 (4.5)	3.6 (4.2)	4.7 (4.1)	4.4 (4.3)	5.6 (3.8)	5.2 (4.2)	4.4 (4.7)	2.2 (3.8)	2.1 (3.7)
LS mean change[a] (SE)	4.4 (0.2)	3.8 (0.2)	2.5 (0.3)	5.4 (0.2)	4.7 (0.2)	3.8 (0.2)	4.7 (0.3)	4.3 (0.3)	5.5 (0.3)	5.2 (0.3)	4.7 (0.3)	2.3 (0.2)	2.0 (0.2)
Difference: vs. placebo (95% CI), *P* value	**1.9 (1.2 to 2.6), *P* < 0.001**	1.3 (0.6 to 2.0), *P* < 0.001											
Difference: FF/VI vs. monotherapy (95% CI), *P* value	0.6 (0.0 to 1.3)[b]			NR	**0.9 (0.3 to 1.5), *P* = 0.002**		0.4 (–0.5 to 1.2)[b]		FF: 0.3 (–0.5 to 1.1)[b] FP: 0.7 (–0.1 to 1.5)[b]				
Difference: FF/VII vs. combination therapy (95% CI), *P* value				0.7 (0.1 to 1.2)[c]	NR							0.2 (–0.2 to 0.07)[b]	

CI = confidence interval; FF = fluticasone furoate; FP = fluticasone propionate; LS = least squares; NR = not reported; S = salmeterol; SD = standard deviation; SE = standard error; VI = vilanterol; vs. = versus.
[a] ANCOVA model with covariates of baseline value, region, sex, age, and treatment group.
[b] Because of the hierarchical testing procedure to account for multiplicity, statistical significance cannot be concluded in this comparison.
[c] Statistical testing was not done for the comparison of FF/VI 200/25 mcg versus FF/VI 100/25 mcg.
Source: Clinical Study Reports.[8-12]

3.6.3 Pulmonary Function

The findings on the various measures for pulmonary function are summarized in Table 22 and Table 23. It is important to note that these findings are not specific to the adult population.

a) FEV_1

Overall, the baseline evening trough FEV_1 values were similar between treatment groups within each study. Change from baseline results showed that placebo was associated with an increase of 222 mL (HZA-827); FP 500 mcg with an increase of 173 mL (HZA-829); FF 100 mcg with an increase ranging from 241 mL (HZA-837) to 382 mL (HZA-863); FF 200 mcg with an increase of 218 mL (HZA-829); FP/S with an increase of 307 mL (HZA-091); FF/VI 100/25 with an increase ranging from 273 mL (HZA-091) to 441 mL (HZA-863); and FF/VI 200/25 with an increase ranging from 388 mL (HZA-829) to 440 mL (HZA-863).

FF/VI 100/25 mcg versus FF 100 mcg: In study HZA-827, no statistically significant difference in evening trough FEV_1 was observed between FF/VI and FF after 12 weeks of treatment (LS mean change, 36 mL; 95% CI, –48 to 120; *P* = 0.405). However, this study finding was inconsistent with those of studies HZA-863 and HZA-837. Evening trough FEV_1 was statistically significantly improved in patients receiving FF/VI compared with FF (LS mean change, 77 mL; 95% CI, 16 to 138; *P* = 0.014) at 12 weeks of treatment and at the last observable end point (LS mean change, 89 mL; 95% CI, 52 to 126; *P* < 0.001) in studies HZA-863 and HZA-837 respectively.

FF/VI 200/25 mcg versus FF 200 mcg: In study HZA-829, baseline evening trough FEV_1 values were similar at baseline and, by week 24, the LS mean change versus FF was 193 mL (95% CI, 108 to 277; *P* < 0.001).

FF/VI 200/25 mcg versus FP 500 mcg: Study HZA-829 reported a statistically significant increase in evening trough FEV_1 of 210 mL after 24 weeks of treatment (95% CI, 127 to 294; *P* < 0.001).

FF/VI 100/25 mcg versus FF/VI 200/25 mcg: Study HZA-863 reported that at 12 weeks, evening trough FEV_1 values were 16 mL greater in patients on high-dose FF/VI than in those on the moderate dose (95% CI, –46 to 77 mL).

FF/VI 100/25 mcg versus FP/S 250/50 mcg: In study HZA-091, the mean change in evening trough FEV_1 following 24 weeks of treatment was found to be less in the FF/VI group compared with the FP/S group (LS mean change, –19 mL; 95% CI, –73 to 34 mL).

b) Weighted Mean FEV_1 (Zero to 24 Hours)

The findings on weighted mean serial FEV_1 are summarized in Table 22 and, in most cases, they appear to be consistent with the evening trough FEV_1.

In study HZA-829, FF/VI 200/25 mcg once daily demonstrated a greater improvement with a LS difference in weighted mean FEV_1 of 136 mL and 206 mL when compared with FF 200 mcg once daily (*P* = 0.048) and FP 500 mcg twice daily (*P* = 0.003), respectively, at 24 weeks. However, a sensitivity analysis that excluded one study site with good clinical practice issues (which had randomized 9% of the ITT population) resulted in a smaller treatment difference when compared with both FF (LS mean change 78 mL; *P* = 0.230) and FP (LS mean change, 124 mL; *P* = 0.047). The findings suggest that this outcome is sensitive to the inclusion of this trial site. Subgroup analysis in the PP population was also no longer statistically significant for this end point.

c) Evening PEF

Overall, an increase from baseline in evening PEF was observed in all active treatment groups.

FF/VI 100/25 mcg versus FF 100 mcg: Although study HZA-827 reported that patients experienced an increase in PEF of 26.4 L/min on FF/VI and 14.1 L/min on FF at week 12, the significance of this treatment effect is uncertain given that this study failed at the first stage of its hierarchical test. Study HZA-863 showed that, after 12 weeks of treatment, FF/VI was associated with statistically significantly higher LS mean increase in evening PEF of 24.2L/min (95% CI, 18 to 30.4; $P < 0.001$) when compared with FF.

FF/VI 200/25 mcg versus FF 200 mcg: In study HZA-829, following 24 weeks of treatment, evening PEF improved by 39.8 L/min and 9.1 L/min for FF/VI and FF, respectively. However, the statistical significance of the between-group treatment effect is uncertain given that this study failed at prior stages of its hierarchical test.

FF/VI 200/25 mcg versus FP 500 mcg: At 12 weeks, study HZA-714 reported that Asian patients on FF/VI had statistically significantly better improvements in evening PEF than those on FP (LS mean change, 28.5 L/min; 95% CI, 20.1 to 36.9; $P < 0.001$). After 24 weeks in study HZA-829, FF/VI was associated with 30.7L/min increase in evening PEF, although statistical significance is uncertain given the pre-specified testing strategy.

FF/VI 100/25 mcg versus FF/VI 200/25 mcg: In study HZA-863, the LS mean difference in change from baseline between FF/VI 200/25 mcg and FF/VI 100/25 mcg was 2.0L/min (95% CI, –4.2 to 8.2).

FF/VI 100/25 mcg versus FP/S 250/50 mcg: There are presently no direct clinical trials that have compared the differences in PEF values with combination therapies.

Morning PEF findings are summarized in Table 22 and, in most cases, they appear to be consistent with evening PEF results. The only exception was study HZA-714, for which claims of statistical significance could not be made, given that the pre-specified hierarchical testing had stopped prior to assessing morning PEF.

TABLE 22: RESULTS OF FEV1 MEASURES IN THE ENTIRE STUDY POPULATION (INTENTION-TO-TREAT)

	HZA-827			HZA-863			HZA-829			HZA-091		HZA-837	
	FF/VI 100/25 mcg	FF 100 mcg	Placebo	FF/VI 200/25 mcg	FF/VI 100/25 mcg	FF 100 mcg	FF/VI 200/25 mcg	FF 200 mcg	FP 500 mcg	FF/VI 100/25 mcg	FP/S 250/25 mcg	FF/VI 100/25 mcg	FF 100 mcg
Evening Trough FEV_1, L													
Total, N	201	205	203	346	346	347	191	193	194	397	389	1,009	1,010
Baseline mean (SD)	2.344 (0.642)	2.290 (0.617)	2.334 (0.626)	1.954 (0.582)	1.985 (0.556)	1.965 (0.598)	2.129 (0.654)	2.190 (0.676)	2.138 (0.673)	NR	NR	2.216 (0.643)	2.193 (0.640)
End of double-blind period,[a] N	200	203	193	339	336	341	193	187	191	399	390	1,001	1,000
End of double-blind period mean (SD)	2.698 (0.804)	2.611 (0.762)	2.576 (0.844)	2.403 (0.771)	2.428 (0.746)	2.358 (0.801)	2.538 (0.856)	2.426 (0.855)	2.310 (0.769)	2.28 (0.775)	2.35 (0.818)	2.560 (0.811)	2.436 (0.828)
Change from baseline mean (SD)	0.354 (0.484)	0.321 (0.452)	0.222 (0.468)	0.440 (0.403)	0.441 (0.435)	0.382 (0.491)	0.388 (0.474)	0.218 (0.495)	0.173 (0.390)	0.273 (0.371)	0.307 (0.446)	0.344 (0.466)	0.241 (0.460)
LS mean change[b] (SE)	0.368 (0.030)	0.332 (0.030)	0.196 (0.031)	0.457 (0.022)	0.441 (0.022)	0.365 (0.022)	0.394 (0.030)	0.201 (0.030)	0.183 (0.030)	0.281 (0.019)	0.300 (0.019)	0.337 (0.013)	0.248 (0.013)
Difference: vs placebo (95% CI), *P* value	**0.172 (0.087 to 0.258), *P* < 0.001**	**0.136 (0.051 to 0.222), *P* = 0.002**											
Difference: FF/VI vs monotherapy (95% CI), *P* value	0.036 (–0.048 to 0.120), *P* = 0.405			NR	**0.077 (0.016 to 0.138), *P* = 0.014**		**FF: 0.193 (0.108 to 0.277), *P* < 0.001 FP: 0.210 (0.127 to 0.294), *P* < 0.001**					**0.089 (0.052 to 0.126), *P* < 0.001**	
Difference: FF/VI vs combination therapy (95% CI), *P* value				0.016 (–0.046 to 0.077)[c,d]	NR					–0.019 (–0.073 to 0.034)[b]			
Weighted Mean FEV_1, L (0 Hours to 24 Hours)													
n	108	106	95	313	314	293	94	83	86	352	347	Not reported	
End of double-blind period mean (SD)	2.861 (0.822)	2.658 (0.780)	2.599 (0.865)	2.447 (0.774)	2.454 (0.722)	2.401 (0.771)	2.716 (0.947)	2.663 (0.851)	2.322 (0.792)	2.343 (0.758)	2.422 (0.818)		
Change from baseline mean (SD)	0.505 (0.515)	0.375 (0.497)	0.246 (0.484)	0.479 (0.401)	0.475 (0.429)	0.387 (0.481)	0.472 (0.576)	0.349 (0.470)	0.229 (0.464)	0.335 (0.355)	0.383 (0.402)		
LS mean change[b] (SE)	0.513 (0.043)	0.398 (0.043)	0.212 (0.046)	0.499 (0.022)	0.474 (0.022)	0.366 (0.023)	0.464 (0.047)	0.328 (0.049)	0.258 (0.048)	0.341 (0.018)	0.377 (0.019)		
Difference: vs. placebo (95% CI), *P* value	**0.302 (0.178 to 0.426), *P* < 0.001**	**0.186 (0.062 to 0.310), *P* = 0.003**											

	HZA-827			HZA-863			HZA-829			HZA-091		HZA-837	
	FF/VI 100/25 mcg	FF 100 mcg	Placebo	FF/VI 200/25 mcg	FF/VI 100/25 mcg	FF 100 mcg	FF/VI 200/25 mcg	FF 200 mcg	FP 500 mcg	FF/VI 100/25 mcg	FP/S 250/25 mcg	FF/VI 100/25 mcg	FF 100 mcg
Difference: FF/VI vs. monotherapy (95% CI), *P* value	0.116 (–0.005 to 0.236), *P* = 0.060			NR	**0.108 (0.045 to 0.171), *P* < 0.001**		**FF: 0.136 (0.001, to 0.270), 0.048 FP: 0.206 (0.073 to 0.339), *P* = 0.003**						
Difference: FF/VI vs. combination therapy (95% CI), *P* value				0.024 (–0.037 to 0.086)[d]	NR					–0.037 (–0.09 to 0.02), *P* = 0.162			

ANCOVA = analysis of covariance; CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; FF = fluticasone furoate; FP = fluticasone propionate; LS = least squares; NR = not reported; PEF = peak expiratory flow; S = salmeterol; SD = standard deviation; SE = standard error; VI = vilanterol; vs. = versus.

[a] In study HZA-837 and HZA-091, the end of double-blind period was instead defined as end point (last on-treatment visit during which pre-dose trough FEV_1 was measured).

[b] ANCOVA model with covariates of baseline value, region, sex, age, and treatment group.

[c] Because of the hierarchical testing procedure to account for multiplicity, statistical significance cannot be concluded in this comparison.

[d] Statistical testing was not done for the comparison of FF/VI 200/25 mcg vs. FF/VI 100/25 mcg.

Source: Clinical Study Reports.[8,9,11-13]

TABLE 23: RESULTS OF PEAK EXPIRATORY FLOW MEASURES IN THE ENTIRE STUDY POPULATION (INTENTION-TO-TREAT)

	HZA-827			HZA-863			HZA-714		HZA-829		
	FF/VI 100/25 mcg	FF 100 mcg	Placebo	FF/VI 200/25 mcg	FF/VI 100/25 mcg	FF 100 mcg	FF/VI 200/25 mcg	FP 500 mcg	FF/VI 200/25 mcg	FF 200 mcg	FP 500 mcg
Evening PEF, L/min											
Total, N	201	205	203	346	346	347	155	154	197	194	195
Baseline mean (SD)	370.2 (122.7)	375.0 (112.8)	367.8 (110.5)	325.7 (111.3)	335.0 (106.7)	344.5 (121.4)	265.2 (95.5)	262.7 (104.9)	342.6 (112.4)	347.8 (120.1)	344.3 (116.1)
End of double-blind period,[a] N	201	204	202	346	345	346	151	148	197	192	194
End of double-blind period mean (SD)	396.6 (117.3)	388.0 (107.3)	367.6 (105.9)	367.6 (111.8)	374.8 (108.2)	359.4 (116.6)	302.2 (98.8)	273.3 (115.0)	382.7 (118.8)	357.7 (120.9)	357.7 (112.9)
Change from baseline, mean (SD)	26.4 (36.2)	12.9 (37.9)	–0.6 (32.2)	41.9 (46.1)	39.7 (43.0)	15.4 (41.7)	38.3 (54.9)	10.0 (49.5)	40.1 (54.4)	9.6 (35.0)	12.8 (39.0)
LS mean change[b] (SE)	26.4 (2.35)	14.1 (2.34)	–1.8 (2.36)	41.7 (2.24)	39.7 (2.24)	15.5 (2.24)	39.1 (3.01)	10.5 (3.03)	39.8 (2.93)	9.1 (2.98)	13.6 (2.96)
Difference: vs. placebo (95% CI), *P* value	**28.2 (21.7 to 34.8), *P* < 0.001**	**15.9 (9.4 to 22.5), *P* < 0.001**									
Difference: FF/VI vs. monotherapy comparator (95% CI), *P* value	12.3 (5.8 to 18.8)[c]			NR	**24.2 (18.0 to 30.4), *P* < 0.001**		**28.5 (20.1 to 36.9), *P* < 0.001**		FF: 30.7 (22.5 to 38.9)[c] FP: 26.2 (18.0 to 34.3)[c]		
Difference: FF/VI vs. combination therapy (95% CI), *P* value				2.0 (–4.2 to 8.2)[d]	NR						
Morning PEF, L/min											
Total, N	201	205	203	346	346	347	155	154	197	194	195
Baseline mean (SD)	361.5 (120.4)	366.3 (111.7)	355.5 (112.3)	317.8 (112.2)	328.0 (109.4)	335.4 (118.6)	262.6 (94.4)	261.4 (103.1)	327.4 (113.3)	332.9 (123.6)	330.2 (114.1)
End of double-blind period,[a] N	201	204	203	345	345	346	153	149	197	193	195
End of double-blind period mean (SD)	394.1 (116.4)	383.0 (107.6)	356.9 (106.8)	365.6 (111.8)	372.4 (109.7)	354.2 (116.7)	309.7 (100.5)	278.8 (117.9)	379.5 (120.4)	352.1 (120.3)	348.3 (114.4)
Change from baseline, mean (SD)	32.6 (41.0)	16.7 (36.5)	1.5 (32.8)	47.7 (46.1)	44.3 (47.2)	19.1 (39.0)	48.3 (56.6)	16.2 (51.2)	52.1 (52.4)	18.6 (36.9)	18.2 (38.7)
LS mean change[b] (SE)	32.9 (2.42)	18.3 (2.41)	–0.4 (2.42)	47.7 (2.25)	44.3 (2.25)	19.1 (2.25)	46.2 (3.07)	14.0 (3.10)	51.8 (2.94)	18.2 (2.97)	18.8 (2.95)
Difference: vs. placebo (95% CI), *P* value	**33.3 (26.5 to 40.0), *P* < 0.001**	**18.7 (12.0 to 25.4), *P* < 0.001**									

	HZA-827			HZA-863			HZA-714		HZA-829		
	FF/VI 100/25 mcg	FF 100 mcg	Placebo	FF/VI 200/25 mcg	FF/VI 100/25 mcg	FF 100 mcg	FF/VI 200/25 mcg	FP 500 mcg	FF/VI 200/25 mcg	FF 200 mcg	FP 500 mcg
Difference: FF/VI vs. monotherapy comparator (95% CI), *P* value	14.6 (7.9, 21.3)[c]			NR	**25.2 (19.0 to 31.5), *P* < 0.001**		32.3 (23.6 to 40.9)[c]		FF: 33.5 (25.3 to 41.7)[c] FP: 32.9 (24.8 to 41.1)[c]		
Difference: FF/VI vs. combination therapy (95% CI), *P* value				3.4 (–2.8 to 9.7)[d]	NR						

CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; FF = fluticasone furoate; FP = fluticasone propionate; LS = least squares; min = minute; NR = not reported; PEF = peak expiratory flow; SD = standard deviation; SE = standard error; VI = vilanterol; vs. = versus.

[a] In study HZA-837 and study HZA-091, the end of the double-blind period was instead defined as the end point (last on-treatment visit during which pre-dose trough FEV-1 was measured).

[b] ANCOVA model with covariates of baseline value, region, sex, age, and treatment group.

[c] Because of the hierarchical testing procedure to account for multiplicity, statistical significance cannot be concluded in this comparison.

[d] Statistical testing was not done for the comparison of FF/VI 200/25 mcg vs. FF/VI 100/25 mcg.

Source: Clinical Study Reports.[8-11]

3.6.4 Use of Rescue Medication

The change in the percentage of rescue-free 24-hour periods was reported in the five lung-function studies, although the findings were not specific to the adult population (Table 24). By the end of the double-blind treatment period, the percentage of rescue medication-free 24-hour periods had improved for patients in all treatment groups, with the greatest relative gains observed in patients receiving combination therapy.

At 12 weeks of double-blind treatment, the improvement in the combination therapy group (FF/VI 100/25 mcg once daily) was statistically significantly greater than the improvement in patients receiving monotherapy (FF 100 mcg once daily) in study HZA-863 (LS mean difference, 12.2%; 95% CI, 7.1 to 17.3), representing an LS mean increase of 0.9 rescue-free medication days per week. This could not be confirmed in study HZA-827, given that hierarchical testing had stopped prior to this outcome. In comparing FF/VI 200/25 mcg once daily to FP 500 mcg once daily in study HZA-714, a non-statistically significant mean improvement of 1% was observed in the number of 24-hour rescue-free periods (95% CI, –7.3 to 9.2; $P = 0.821$).

By week 24 of study HZA-829, patients in the FF/VI 200/25 mcg once-daily group demonstrated a LS mean improvement that was 11.7% greater than that observed in the FF 200 mcg once-daily group ($P < 0.001$) and 6.3% greater than that observed in the FP 500 mcg twice-daily group ($P = 0.067$). This equated to an extra 0.8 and 0.4 rescue-free medication days per week, respectively. The clinical relevance of these findings is not known.

The difference in rescue-free medication periods between combination therapies remains unknown, as study HZA-091 did not measure and report on this outcome.

TABLE 24: RESULTS OF PERCENTAGE OF RESCUE-FREE 24-HOUR PERIODS IN THE ENTIRE STUDY POPULATION (INTENTION-TO-TREAT)

	HZA-827			HZA-863			HZA-714		HZA-829		
	FF/VI 100/25 mcg	FF 100 mcg	Placebo	FF/VI 200/25 mcg	FF/VI 100/25 mcg	FF 100 mcg	FF/VI 200/25 mcg	FP 500 mcg	FF/VI 200/25 mcg	FF 200 mcg	FP 500 mcg
Total, N	201	205	203	346	346	347	155	154	197	194	195
Baseline mean (SD)	13.4 (27.4)	15.3 (29.2)	14.5 (29.9)	5.8 (16.0)	4.4 (12.6)	4.4 (12.1)	10.3 (24.7)	12.4 (27.8)	7.6 (19.2)	7.8 (20.7)	6.3 (18.0)
End of double-blind period,[a] N	201	204	202	346	345	346	155	152	197	193	194
End of double-blind period mean (SD)	50.9 (37.8)	40.9 (37.9)	32.8 (36.9)	41.0 (38.8)	39.2 (37.7)	27.7 (31.7)	43.4 (41.2)	42.7 (40.4)	45.9 (39.1)	34.4 (37.4)	37.9 (36.6)
Change from baseline mean (SD)	37.5 (37.6)	25.5 (33.1)	18.3 (34.5)	35.2 (37.9)	34.8. (36.2)	23.3 (29.9)	33.0 (39.0)	30.8 (38.2)	38.3 (36.4)	26.6 (34.4)	31.8 (35.2)
LS mean change[a] (SE)	37.1 (2.3)	26.5 (2.3)	17.8 (2.3)	35.8 (1.9)	34.8 (1.9)	22.6 (1.8)	32.4 (3.0)	31.5 (3.0)	38.2 (2.4)	26.6 (2.5)	31.9 (2.5)
Difference: vs. placebo (95% CI), *P* value	**19.3 (13.0, 25.6), *P* < 0.001**	**8.7 (2.4, 15.0,) *P* =0.007**									
Difference: FF/VI vs. monotherapy (95% CI), *P* value	10.6 (4.3 to 16.8)[b]			NR	**12.2 (7.1 to 17.3), *P* < 0.001**		1.0 (–7.3 to 9.2), *P* = 0.821		**FF: 11.7 (4.9, 18.4), *P* < 0.001** FP: 6.3 (–0.4 to 13.1), *P* = 0.067		
Difference: FF/VI vs. combination therapy (95% CI)				0.9 (–4.2 to 6.1)[c]	NR						

CI = confidence interval; FF = fluticasone furoate; FP = fluticasone propionate; LS = least squares; NR = not reported; SD = standard deviation; SE = standard error; VI = vilanterol; vs. = versus.
[a] ANCOVA model with covariates of baseline value, region, sex, age, and treatment group.
[b] Because of the hierarchical testing procedure to account for multiplicity, statistical significance cannot be concluded in this comparison.
[c] Statistical testing was not done for the comparison of FF/VI 200/25 mcg vs. FF/VI 100/25 mcg.
Source: Clinical Study Reports.[8-11]

3.6.5 Health Care Resource Utilization

Among the trials that recorded health care resource utilization, reports on unscheduled health care resource use were low across all treatment groups and studies. In studies HZA-827 and HZA-714, additional resources were reported for both physician office or practice visits and urgent care or outpatient clinic visits over the 12-week treatment duration (Table 25). The incidence was generally lower in patients on FF/VI 100/25 mcg once daily than in those receiving FF 100 mcg once daily, although the clinical significance of this finding is uncertain.

During 24 weeks of treatment, unscheduled resource utilization related to severe asthma exacerbation included two physician office or practice visits, both from the FP 500 mcg twice-daily group; one unscheduled emergency room visit from the FF 200 mcg once-daily group; and one in-patient hospitalization in the FF 200 mcg once-daily group in study HZA-829. Health care visits were similarly low in study HZA-091 (Table 25).

TABLE 25: RESULTS OF UNSCHEDULED HEALTH CARE CONTACTS IN THE ENTIRE STUDY POPULATION (INTENTION-TO-TREAT)

	HZA-827			HZA-714		HZA-829			HZA-091	
	FF/VI 100/25 mcg	FF 100 mcg	Placebo	FF/VI 200/25 mcg	FP 500 mcg	FF/VI 200/25 mcg	FF 200 mcg	FP 500 mcg	FF/VI 100/25 mcg	FP/S 250/25 mcg
Total, N	201	205	203	155	154	197	194	195	403	403
Number of home visits (day), mean (SD)	0	0	0	NR		0	0 (0.07)	0	0	0 (0.05)
Related to severe exacerbation, mean (SD)	0	0	0			0	0	0	0	0
Number of home visits (night), mean (SD)	0	0	0	NR		0	0	0	0	0
Related to severe exacerbation, mean (SD)	0	0	0			0	0	0	0	0
Number of physician office visits, mean (SD)	0 (0.10)	0 (0.39)	0 (0.24)	0 (0.08)	0 (0.18)	0	0 (0.10)	0.1 (0.45)	0 (0.29)	0 (0.18)
Related to severe exacerbation, mean (SD)	0 (0.07)	0 (0.37)	0 (0.21)	0 (0.08)	0 (0.18)	0	0	0 (0.1)	0 (0.15)	0 (0.10)
Number of urgent care/outpatient clinic visit, mean (SD)	0	0 (0.07)	0 (0.07)	0 (0.16)	0 (0.11)	0	0	0	0 (0.05)	0 (0.05)
Related to severe exacerbation	0	0 (0.07)	0 (0.07)	0	0 (0.08)	0	0	0	0 (0.05)	0 (0.05)
Number of ER visits	0	0	0	0	0 (0.08)	0	0 (0.07)	0	0 (0.15)	0 (0.14)
Related to severe exacerbation	0	0	0	0	0 (0.08)	0	0 (0.07)	0	0 (0.07)	0 (0.10)
Number of in-patient hospital days (ICU/ general)	0	0	0	0.1 (1.12)	0.1 (0.97)	0	0 (0.29)	0	0 (0.2)	0 (0.39)
Related to severe exacerbation	0	0	0	0	0.1 (0.97)	0	0 (0.29)	0	0 (0.1)	0 (0.39)

ER = emergency room; FF = fluticasone furoate; FP = fluticasone propionate; ICU = intensive care unit; NR = not reported; S = salmeterol; SD = standard deviation; VI = vilanterol.
Source: Clinical Study Reports.[8,10-12]

3.6.6 Other Efficacy Outcomes

a) Days of Missed Work or School

The number of days of missed work was not measured in the included studies.

b) Patient Adherence and Satisfaction

In studies HZA-827 and HZA-863, the percentage of patients using the inhaler correctly at baseline was high (≥ 94%), and remained high by the fourth week of treatment (≥ 99%). Correct inhaler use was not reported in studies HZA-714, HZA-829, HZA-091, HZA-837, or HZA-839.

All trials reported on a measure of adherence. The value was generally high across all treatment groups. Overall, the majority of patients (72% to 87%) had a range of adherence between 95% and 105%.

TABLE 26: SUMMARY OF INHALER USE ASSESSMENT

	HZA-827			HZA-863		
	FF/VI 100/25 mcg	FF 100 mcg	Placebo	FF/VI 200/25 mcg	FF/VI 100/25 mcg	FF 100 mcg
Did patient use inhaler correctly at baseline?						
N	201	205	203	346	346	347
Yes, n (%)	188 (94)	196 (96)	194 (96)	334 (97)	337 (97)	340 (98)
No, n (%)	13 (6)	9 (4)	9 (4)	12 (3)	9 (3)	7 (2)
Did patient use inhaler correctly at subsequent visits? (Week 4)						
N	195	199	175	335	329	325
Yes, n (%)	195 (100)	199 (100)	175 (100)	332 (> 99)	327 (> 99)	321 (99)
No, n (%)	0	0	0	3 (< 1)	2 (< 1)	4 (1)

FF = fluticasone furoate; VI = vilanterol.
Source: Clinical Study Reports.[8,9]

TABLE 27: SUMMARY OF TREATMENT ADHERENCE

Study and Treatment Group	Inhaler	Adherence, %			Range of Adherence, n (%)				
		N	Mean (SD)	Median (min, max)	< 80%	≥ 80 to < 95%	≥ 95 to ≤ 105%	> 105 to ≤ 120%	> 120%
HZA-827									
FF/VI 100/25 mcg	NDPI	201	98.7 (6.46)	100 (45, 136)	4 (2)	20 (10)	167 (83)	9 (4)	1 (< 1)
FF 100 mcg	NDPI	205	98.8 (6.15)	100 (74, 152)	2 (< 1)	25 (12)	174 (85)	3 (1)	1 (< 1)
Placebo	NDPI	201	97.5 (6.60)	100 (59, 120)	5 (2)	35 (17)	154 (77)	7 (3)	0
HZA-863									
FF/VI 200/25 mcg	NDPI	346	98.6 (6.08)	100 (69, 160)	3 (< 1)	50 (14)	284 (82)	7 (2)	2 (< 1)
FF/VI 100/25 mcg	NDPI	346	98.9 (6.77)	100 (74, 179)	3 (< 1)	42 (12)	292 (84)	7 (2)	2 (< 1)
FF 100 mcg	NDPI	347	98.7 (6.93)	100 (67, 175)	4 (1)	46 (13)	281 (81)	14 (4)	2 (< 1)
HZA-714									
FF/VI 200/25 mcg	NDPI Diskus	154 154	95.7 (9.72) 94.3 (9.53)	98.8 (11, 107) 97.0 (15, 114)	6 (4) 6 (4)	36 (23) 55 (36)	109 (71) 91 (59)	3 (2) 2 (1)	0 0
FP 500 mcg	NDPI Diskus	154 154	96.4 (8.08) 95.4 (8.68)	97.7 (43, 113) 97.0 (26, 111)	5 (3) 4 (3)	36 (23) 45 (29)	107 (69) 101 (66)	6 (4) 4 (3)	0 0
HZA-829									
FF/VI 200/25 mcg	NDPI Diskus	196 195	98.4 (5.42) 97.0 (6.33)	100 (68, 124) 98.8 (63, 127)	3 (2) 5 (3)	25 (13) 38 (19)	164 (84) 149 (76)	3 (2) 2 (1)	1 (< 1) 1 (< 1)
FF 200 mcg	NDPI Diskus	191 191	98.5 (5.33) 96.1 (6.96)	100 (76, 133) 98.2 (50, 106)	3 (2) 8 (4)	28 (15) 41 (21)	154 (81) 139 (73)	5 (3) 3 (2)	1 (< 1) 0
FP 500 mcg	NDPI Diskus	194 194	97.9 (10.11) 95.2 (8.31)	99.4 (42, 200) 97.9 (35, 107)	4 (2) 11 (6)	32 (16) 42 (22)	153 (79) 139 (72)	4 (2) 2 (1)	1 (< 1) 0
HZA-091									
FF/VI 200/25 mcg	NDPI Diskus	403	97.0 (9.17) 94.1 (9.44)	NR (47, 200) NR (36, 118)	15 (4) 28 (7)	72 (18) 117 (29)	306 (76) 254 (63)	9 (2) 4 (< 1)	1 (< 1) 0
FP/S 250/50 mcg	NDPI Diskus	403	96.0 (9.04) 94.2 (9.28)	NR (14, 111) NR (11, 112)	20 (5) 23 (6)	77 (19) 111 (28)	294 (74) 262 (66)	9 (2) 4 (1)	0 0
HZA-837									
FF/VI 100/25 mcg	NDPI	1009	98.0 (5.78)	NR (24, 133)	13 (1)	120 (13)	769 (83)	19 (2)	2 (< 1)
FF 100 mcg	NDPI	1010	98.3 (6.48)	NR (59, 200)	11 (1)	118 (13)	773 (84)	18 (2)	2 (< 1)
HZA-839									
FF/VI 200/25 mcg	NDPI Diskus	202	99.4 (8.65) 97.8 (10.09)	NR (56,200) NR (50, 200)	1 (< 1) 4 (2)	18 (9) 26 (13)	176 (87) 169 (84)	6 (3) 2 (< 1)	1 (< 1) 1 (< 1)
FF/VI 100/25 mcg	NDPI Diskus	201	99.9 (14.30) 97.6 (10.45)	NR (59, 250) NR (40, 200)	1 (< 1) 5 (3)	25 (13) 32 (16)	166 (83) 158 (79)	4 (2) 3 (2)	4 (2) 2 (1)
FP 500 mcg	NDPI Diskus	100	97.6 (6.21) 96.3 (8.21)	NR (73, 107) NR (54, 107)	6 (6) 5 (5)	6 (6) 10 (10)	87 (87) 84 (84)	1 (1) 1 (1)	0 0

FF = fluticasone furoate; FP = fluticasone propionate; NDPI = novel dry powder inhaler; NR = not reported; S = salmeterol; SD = standard deviation; VI = vilanterol.
Source: Clinical Study Reports.[8-14]

c) Number of Asthma Symptom-free Days

The change in the number of symptom-free days was not reported specifically among the adult population. Instead, as a secondary efficacy end point in most lung-function trials, this outcome was reported with respect to the overall study population, which included both adolescent and adult patients (Table 28). By the end of the treatment period, the percentage of symptom-free 24-hour periods was found to have improved for all patients irrespective of treatment group assignment.

By week 12 of study HZA-863, the change in symptom-free 24-hour periods was greatest in patients on combination therapy. The LS mean difference versus FF 100 mcg once-daily monotherapy was statistically significant at 7.8%. The improvement in percentage of symptom-free 24-hour periods equated to an LS mean increase of 0.5 days per week. For the same comparison at the same time point, statistical significance in study HZA-827 could not be concluded given the statistical testing strategy. Similarly, the statistical significance of study HZA-714 comparing FF/VI 200/25 mcg once daily to FP 500 mcg twice daily could not be determined because the hierarchical testing was stopped before this outcome.

By week 24 of study HZA-829, patients on FF/VI 200/25 mcg once daily demonstrated a LS mean improvement that was 8.4% greater than patients on FF 200 mcg once daily (P = 0.01), and 4.9% greater than patients on FP 500 mcg twice daily (P = 0.137). This equated to an extra 0.6 days per week and 0.3 symptom-free days per week, respectively. The clinical relevance of the findings that were statistically significant is not known.

The difference in symptom-free periods between combination therapies has not been studied in the existing trials.

TABLE 28: RESULTS OF PERCENTAGE OF SYMPTOM-FREE 24-HOUR PERIODS IN THE ENTIRE STUDY POPULATION (INTENTION-TO-TREAT)

	HZA-827			HZA-863			HZA-714		HZA-829		
	FF/VI 100/25 mcg	FF 100 mcg	Placebo	FF/VI 200/25 mcg	FF/VI 100/25 mcg	FF 100 mcg	FF/VI 200/25 mcg	FP 500 mcg	FF/VI 200/25 mcg	FF 200 mcg	FP 500 mcg
Baseline											
N	201	205	203	346	346	347	155	154	194	197	195
Mean (SD)	5.0 (15.2)	5.8 (16.5)	3.5 (12.8)	4.6 (15.4)	3.8 (14.4)	4.8 (14.6)	5.8 (18.4)	6.4 (20.8)	5.1 (15.2)	4.7 (16.1)	2.7 (9.8)
Week 1 to end of double-blind period											
N	201	204	202	346	345	346	155	152	197	193	194
Mean (SD)	37.5 (36.3)	25.2 (32.6)	19.1 (28.7)	33.7 (36.2)	30.9 (36.7)	24.3 (31.0)	31.5 (38.2)	26.7 (34.6)	34.4 (37.9)	25.8 (33.9)	26.9 (33.7)
Change from baseline, mean (SD)	32.5 (36.4)	19.5 (30.0)	15.6 (29.9)	29.0 (34.8)	27.1 (34.4)	19.5 (28.4)	25.8 (36.4)	20.3 (33.0)	29.4 (34.9)	21.1 (31.4)	24.4 (32.3)
LS mean change[a] (SE)	32.5 (2.1)	20.4 (2.1)	14.6 (2.2)	29.0 (1.7)	27.2 (1.7)	19.4 (1.7)	25.4 (2.7)	20.6 (2.8)	29.3 (2.29)	21.0 (2.32)	24.5 (2.31)
Difference: vs. placebo (95% CI), *P* value	**18.0 (12.0 to 23.9), *P* < 0.001**	5.8 (–0.1 to 11.8), *P* = 0.055									
Difference: FF/VI vs. monotherapy (95% CI), *P* value	12.1 (6.2 to 18.1)[b]			NR	**7.8 (2.9 to 12.6), *P* = 0.002**		4.9 (–2.8 to 12.5)[b]		**FF: 8.4 (2.0 to 14.8), *P* = 0.010** FP: 4.9 (–1.6 to 11.3)[b]		
Difference: FF/VI vs. combination therapy (95% CI), *P* value				1.9 (–3.0 to 6.7)[c]	NR						

ANCOVA = analysis of covariance; CI = confidence interval; FF = fluticasone furoate; FP = fluticasone propionate; LS = least squares; NR = not reported; SD = standard deviation; SE = standard error; VI = vilanterol; vs. = versus.
[a] ANCOVA model with effects due to baseline percentage, region, sex, age, and treatment group.
[b] Because of the hierarchical testing procedure to account for multiplicity, statistical significance cannot be concluded in this comparison.
[c] Statistical testing was not done for the comparison of FF/VI 200/25 mcg versus FF/VI 100/25 mcg.
Source: Clinical Study Reports.[8-11]

d) Incidence of Dyspnea

Dyspnea was not measured or reported in the included studies.

e) Incidence of Nocturnal Awakening

In the lung-function trials, patients recorded nighttime asthma symptom scores — which captured awakening and sleep disturbances — daily in their diaries. However, these findings were not reported in the available reports.

3.7 Harms

Only those harms identified in the review protocol are reported in Section 2.2.1 (Protocol).

3.7.1 Adverse Events

In the 52-week safety study (HZA-839), the percentage of patients experiencing an AE ranged from 66% to 73% across treatment groups (Table 31). Similar percentages were reported in the exacerbation event-driven study, HZA-837 (treatment duration of 24 weeks to 76 weeks). AEs were reported in 65% of patients in the FF group and in 63% of patients in the FF/VI group (Table 30). In the lung-function trials (i.e., 12 weeks to 24 weeks in duration), the proportion of patients experiencing an AE ranged from 25% to 53% (Table 29). Generally, the most common AEs across all trials were nasopharyngitis, headaches, and upper respiratory tract infections.

3.7.2 Serious Adverse Events

In study HZA-839, the proportion of patients experiencing SAEs during the treatment period ranged from 7% in patients treated with FP 500 mcg twice daily to < 1% in patients treated with FF/VI 200/25 mcg once daily (Table 31). Of these cases, only one was considered drug-related by the investigator (i.e., worsening hepatitis).

The rates of SAEs in study HZA-837 were 4% in the FF/VI 100/25 mcg once-daily group and 3% in the FF 100 mcg once-daily group (Table 30). Among these, four were deemed drug-related by the investigator: three (< 1%) were patients in the FF 100 mcg group (i.e., AEs relating to pleurisy, asthma, and non-cardiac chest pain) and one (< 1%) was in the FF/VI 100/25 mcg group (i.e., tachyarrhythmia). In total, 17 patients had SAEs that were considered asthma-related: seven (< 1%) were patients in the FF 100 mcg group and 10 (< 1%) were in the FF/VI 100/25 mcg group.

In the 12-week and 24-week lung-function trials, the proportion of patients experiencing SAEs ranged from 0% to 3% (Table 29). Within studies, the proportion of patients experiencing SAEs between treatment groups was not remarkably different.

3.7.3 Withdrawals Due to Adverse Events

The proportion of patients who withdrew due to an adverse event (WDAE) over a 52-week treatment period ranged from 1% to 6% across treatment groups in study HZA-839 (Table 31). The most common reasons for study withdrawal related to asthma exacerbation or cough. Overall, of the 14 patients who had AEs that led to withdrawal, 10 had AEs that were considered drug-related by the investigator. In the other studies, rates of withdrawal were low (i.e., ranging from 0% to 4%) and relatively balanced between treatment groups (Table 29, Table 30).

3.7.4 Mortality

In most trials, no deaths occurred, with the exception of study HZA-837 (Table 30). Three deaths were recorded: two patients died during the double-blind treatment, one in each treatment group (i.e., FF 100 mcg and FF/VI 100/25 mcg), and one died during the post-treatment follow-up in the FF group. These were all considered non–asthma related: one was due to endogenous intoxication and pneumonia; the other was due to injuries sustained from a car accident; and the last was a case of stage IV lung cancer, whereby the patient was withdrawn from the study and monitored over the follow-up period.

3.7.5 Notable Harms

During the on-treatment period, infections and infestations (System Organ Class Preferred Term) were frequent, ranging from 11% to 46%. The lowest rates were recorded in the 12-week study, HZA-827 (11% to 17%), while the most frequent were registered in the variable duration study, HZA-837 (44% to 46%), and the 52-week study, HZA-839 (36% to 46%). The rate of notable harms was similarly proportional to the studies' durations. Across studies, local steroid effects ranged from less than 1% to 15%, with the most commonly reported complications being oropharyngeal pain and dysphonia. Across most studies and treatment groups, cardiovascular complications were generally rare, ranging from less than 1% to 4%. The only exception was study HZA-839, in which the cardiovascular-related harms ranged from 10% in patients receiving FP 500 mcg twice daily to 18% in patients receiving FF/VI 200/25 mcg once daily.

TABLE 29: HARMS — LUNG-FUNCTION PROFILE STUDIES

	HZA-827			HZA-863			HZA-714		HZA-829			HZA-091	
	FF/VI 100/25 mcg (n = 201)	FF 100 mcg (n = 205)	Placebo (n = 203)	FF/VI 200/25 mcg (n = 346)	FF/VI 100/25 mcg (n = 346)	FF 100 mcg (n = 347)	FF/VI 200/25 mcg (n = 155)	FP 500 mcg (n = 154)	FF/VI 200/25 mcg (n = 197)	FF 200 mcg (n = 194)	FP 500 mcg (n = 195)	FF/VI 100/25 mcg (n = 403)	FP/S 250/50 mcg (n = 403)
AEs (On Treatment)													
Patients with > 0 AEs, N (%)	59 (29)	52 (25)	43 (21)	123 (36)	127 (37)	127 (37)	40 (26)	41 (27)	92 (47)	90 (46)	97 (50)	213 (53)	198 (49)
Most common AEs[a]													
Nasopharyngitis	20 (10)	14 (7)	15 (7)	25 (7)	22 (6)	26 (7)	6 (4)	6 (4)	25 (13)	27 (14)	39 (20)	46 (11)	46 (11)
Headache	10 (5)	9 (4)	8 (4)	29 (8)	29 (8)	32 (9)	1 (< 1)	1 (< 1)	11 (6)	13 (7)	15 (8)	34 (8)	41 (10)
URTI	3 (1)	4 (2)	0	7 (2)	8 (2)	12 (3)	13 (8)	18 (12)	3 (2)	2 (1)	4 (2)	26 (6)	16 (4)
Bronchitis	1 (< 1)	0	3 (1)	7 (2)	2 (< 1)	6 (2)	1 (< 1)	0	7 (4)	6 (3)	6 (3)	9 (2)	9 (2)
Influenza	0	0	0	9 (3)	10 (3)	4 (1)	2 (1)	0	5 (3)	8 (4)	7 (4)	3 (< 1)	2 (< 1)
Cough	0	1 (< 1)	2 (< 1)	4 (1)	7 (2)	6 (2)	0	2 (1)	3 (2)	6 (3)	13 (7)	15 (4)	13 (3)
Oropharyngeal pain	4 (2)	4 (2)	3 (1)	7 (2)	6 (2)	4 (1)	4 (3)	1 (< 1)	4 (2)	8 (4)	7 (4)	11 (3)	9 (2)
SAEs													
Patients with > 0 SAEs, N (%)[b]	0	1 (< 1)	0	1 (< 1)	4 (1)	3 (< 1)	1 (< 1)	2 (1)	6 (3)	1 (< 1)	2 (1)	4 (< 1)	5 (1)
WDAEs													
WDAEs, N (%)	2 (< 1)	0	1 (< 1)	3 (< 1)	3 (< 1)	4 (1)	2 (1)	2 (1)	7 (4)	3 (2)	2 (1)	6 (1)	8 (2)
Deaths													
Number of deaths, N (%)	0	0	0	0	0	0	0	0	0	0	0	0	0
Notable Harms (On-Treatment and Post-Treatment)													
Local steroid effects:	13 (6)	10 (5)	3 (1)	15 (4)	14 (4)	10 (3)	4 (3)	1 (< 1)	19 (10)	12 (6)	16 (8)	20 (5)	16 (4)
Oropharyngeal pain	4 (2)	4 (2)	3 (1)	7 (2)	7 (2)	5 (1)	4 (3)	1 (< 1)	4 (2)	8 (4)	7 (4)	11 (3)	9 (2)
Dysphonia	5 (2)	3 (1)	0	3 (< 1)	5 (1)	3 (< 1)	0	0	6 (3)	2 (1)	4 (2)	7 (2)	4 (< 1)
Oral candidiasis	4 (2)	2 (< 1)	0	4 (1)	2 (< 1)	1 (< 1)	0	0	4 (2)	2 (1)	4 (2)	1 (< 1)	3 (< 1)
Oropharyngeal candidiasis	1 (< 1)	2 (< 1)	0	1 (< 1)	0	1 (< 1)	0	0	5 (3)	1 (< 1)	2 (1)	0	0
Cardiovascular effects:[c]	4 (2)	2 (< 1)	2 (< 1)	1 (< 1)	6 (2)	3 (< 1)	3 (2)	1 (< 1)	4 (2)	5(3)	5 (3)	12 (3)	15 (4)
Extrasystoles	1 (< 1)	0	0	0	0	0	0	0	0	1 (< 1)	1 (< 1)	0	0
Hypertension	0	0	0	0	2 (< 1)	2 (< 1)	0	0	1 (< 1)	2 (1)	4 (2)	5 (1)	2 (< 1)
Infections and infestations (on-treatment only)	34 (17)	31 (15)	22 (11)	66 (19)	62 (18)	71 (20)	26 (17)	25 (16)	59 (30)	61 (31)	70 (36)	124 (31)	112 (28)
Bronchitis	1 (< 1)	0	3 (1)	7 (2)	2 (< 1)	6 (2)	1 (< 1)	0	7 (4)	6 (3)	6 (3)	9 (2)	9 (2)
Pneumonia	0	0	0	0	1 (< 1)	2 (< 1)	2 (1)	0	1 (< 1)	1 (< 1)	0	0	2 (< 1)

AE = adverse event; FF = fluticasone furoate; FP = fluticasone propionate; S = salmeterol; SAE = serious adverse event; URTI = upper respiratory tract infection; VI = vilanterol; WDAE = withdrawal due to adverse event.
[a] Frequency > 5%.
[b] The rate of specific types of SAE had a frequency < 1% within each treatment group.
[c] Cardiovascular effects include atrial fibrillation, chest discomfort, chest pain, extrasystoles, hypertension, increased heart rate, increased blood pressure, edema peripheral, palpitations, presyncope, and tachycardia.
Source: Clinical Study Reports.[8-12]

TABLE 30: HARMS — ASTHMA EXACERBATION STUDIES

	HZA-837	
	FF/VI 100/25 mcg (n = 1009)	FF 100 mcg (n = 1010)
AEs		
Patients with > 0 AEs, N (%)	636 (63)	652 (65)
Most common AEs[a]		
Nasopharyngitis	155 (15)	131 (13)
Headache	188 (19)	179 (18)
URTI	73 (7)	93 (9)
Bronchitis	59 (6)	74 (7)
Influenza	50 (5)	38 (4)
Cough	55 (5)	64 (6)
Oropharyngeal pain	41 (4)	55 (5)
SAEs		
Patients with > 0 SAEs,[b] N (%)	41 (4)	29 (3)
WDAEs		
WDAEs, N (%)	16 (2)	19 (2)
Deaths		
Number of deaths, N (%)	1[c]	2 (< 1)[c]
Notable harms		
Local steroid effects:	78 (8)	83 (8)
Oropharyngeal pain	41 (4)	55 (5)
Dysphonia	24 (2)	16 (2)
Oral candidiasis	8 (< 1)	9 (< 1)
Oropharyngeal candidiasis	0	1 (< 1)
Cardiovascular effects:[d]	55 (5)	55 (5)
Extrasystoles	2 (< 1)	1 (< 1)
Hypertension	24 (2)	17 (2)
Infections and infestations (on-treatment only)	461 (46)	440 (44)
Bronchitis	59 (6)	74 (7)
Pneumonia	10 (< 1)	8 (< 1)

AE = adverse event; FF = fluticasone furoate; SAE = serious adverse event; URTI = upper respiratory tract infection; VI = vilanterol; WDAE = withdrawal due to adverse event.

[a] Frequency > 5%.

[b] The rate of specific types of SAEs had a frequency < 1% within each treatment group.

[c] Mortality was deemed not treatment- or asthma-related. One of the patients in the FF 100 mcg group died during the post-treatment period.

[d] Cardiovascular effects include atrial fibrillation, chest discomfort, chest pain, extrasystoles, hypertension, increased heart rate, increased blood pressure, oedema peripheral, palpitations, presyncope, and tachycardia.

Source: Clinical Study Report.[13]

TABLE 31: HARMS — SAFETY AND TOLERABILITY OUTCOMES ONLY

	HZA-839		
	FF/VI 200/25 mcg (n = 202)	FF/VI 100/25 mcg (n = 201)	FP 500 mcg (n = 100)
AEs			
Patients with > 0 AEs, N (%)	134 (66)	139 (69)	73 (73)
Most common AEs[a]			
Nasopharyngitis	19 (9)	25 (12)	10 (10)
Headache	35 (17)	39 (19)	23 (23)
URTI	30 (15)	34 (17)	18 (18)
Bronchitis	9 (4)	7 (3)	5 (5)
Influenza	3 (1)	1 (< 1)	2 (2)
Cough	11 (5)	9 (4)	13 (13)
Oropharyngeal pain	12 (6)	7 (3)	11 (11)
Pyrexia	13 (6)	8 (4)	6 (6)
Oral candidiasis	11 (5)	12 (6)	2 (2)
Back pain	13 (6)	8 (4)	3 (3)
Extrasystoles	15 (7)	4 (2)	3 (3)
Abdominal pain upper	11 (5)	8 (4)	1 (1)
Respiratory tract infection	5 (2)	6 (3)	7 (7)
Sinusitis	4 (2)	9 (4)	5 (5)
SAEs			
Patients with > 0 SAEs,[b] N (%)	1 (< 1)	3 (1)	7 (7)
WDAEs			
WDAEs, N (%)	3 (1)	5 (2)	6 (6)
Deaths			
Number of deaths, N (%)	0	0	0
Notable harms			
Local steroid effects:	31 (15)	24 (12)	15 (15)
Oropharyngeal pain	13 (6)	7 (3)	11 (11)
Dysphonia	6 (3)	8 (4)	3 (3)
Oral candidiasis	11 (5)	12 (6)	2 (2)
Oropharyngeal candidiasis	2 (< 1)	3 (1)	1 (1)
Cardiovascular effects:[c]	37 (18)	24 (12)	10 (10)
Extrasystoles	16 (8)	5 (2)	3(3)
Hypertension	5 (2)	3 (1)	2 (2)
Infections and infestations (on-treatment only)	72 (36)	87 (43)	46 (46)
Bronchitis	9 (4)	7 (3)	5 (5)
Pneumonia	4 (2)	1 (< 1)	1 (1)

AE = adverse event; FF = fluticasone furoate; FP = fluticasone propionate; SAE = serious adverse event; URTI = upper respiratory tract infection; VI = vilanterol; WDAE = withdrawal due to adverse event.

[a] Frequency > 5%.

[b] The rate of specific types of SAE had a frequency < 1% within each treatment group.

[c] Cardiovascular effects include atrial fibrillation, chest discomfort, chest pain, extrasystoles, hypertension, increased heart rate, increased blood pressure, edema peripheral, palpitations, presyncope, and tachycardia.

Source: Clinical Study Report.[14]

4. DISCUSSION

4.1 Summary of Available Evidence

Seven manufacturer-sponsored, phase 3, multi-centre, randomized, double-blind trials were conducted that met the inclusion criteria for this systematic review. The included studies compared the efficacy and safety of one or both fixed doses of FF/VI (100/25 mcg or 200/25 mcg) to FP/S, FF, FP and/or placebo. The trials included patients diagnosed with asthma aged 12 years or older, with a FEV_1 reversibility of ≥ 12% and ≥ 200 mL following SABA inhalation and who were on ICS, with or without LABA, for 12 or more weeks before screening, with a stable dose maintained for four weeks or longer. In part, the patient population enrolled in these trials was consistent with the Health Canada indication, with the exception of including adolescents in the trials. According to the clinical expert consulted on this review, the inclusion of adolescents in the trial is unlikely to affect study findings as, except for studies HZA-827, HZA-837, and HZA-839, the proportion of adolescents was less than 10%.

The mean age of trial participants ranged from 38.5 years to 47.3 years, with a majority of females. Study patients had, on average, a history of asthma for more than 10 years. Mean pre-bronchodilator FEV_1, at screening, ranged from 1.646 L to 2.353 L. Per the clinical expert consulted on this review, this would represent the typical adult population with asthma in which a combination ICS/LABA inhaler would be suitable.

4.2 Interpretation of Results

4.2.1 Efficacy

To support regulatory requirements, trials comparing the combination to one of the active components were required to show the contribution of each component present within the combination and to ascertain whether a clinically meaningful benefit was present in the combination therapy over a single ingredient.[27]

Treatment effect on asthma exacerbation, which is both a safety and efficacy outcome, is of importance to patients according to received patient input (0).Overall, in patients with a lower risk of experiencing an asthma exacerbation (i.e., no history of an exacerbation in the past six months), the incidence of severe exacerbation was low, ranging from 0% to 4%. In patients at higher risk of an exacerbation (i.e., study HZA-837, which recruited patients with a history of an exacerbation in the previous year), the Cox proportional analysis of time to first asthma exacerbation showed a decreased adjusted probability by 52 weeks: 15.9% for FF 100 mcg versus 12.8% for FF/VI 100/25 mcg, which represents a hazard ratio of 0.795 (P = 0.036). This equates to a relative risk reduction of approximately 20% and an absolute risk reduction of 3.1%. The rate of severe asthma exacerbation per patient per year was 0.14 and 0.19 in the FF/VI 100/25 mcg and FF 100 mcg arm, respectively (corresponding to one in every seven and every five years, respectively). According to the Health Canada reviewer's report, this corresponds to patients having to take FF/VI for five years before seeing an incremental benefit from the addition of the LABA.[39] The clinical relevance of incorporating VI into FF to provide a 3.1% absolute reduction in severe exacerbation or to wait five years to prevent a severe exacerbation is unknown.

With respect to lung function, study HZA-091 failed to demonstrate superiority of FF/VI 100/25 mcg once daily to FP/S 250/50 mcg twice daily in weighted mean 24-hour serial FEV_1 (LS mean difference, –37 mL; 95% CI, –0.09 to 0.02; P = 0.162). As such, no further statistical analysis would be appropriate for the other outcomes in this study, given the hierarchical testing strategy.

In comparing between the two doses of FF/VI (100/25 versus 200/25 mcg), it is not clear whether a statistical difference exists on lung-function measures. Only study HZA-863 compared both doses, but did not define this comparison between drug strengths a priori. When compared with monotherapy, some evidence exists — albeit not robust — that FF/VI is statistically significantly different to monotherapy. For instance, the LS mean difference between FF/VI 100/25 mcg and FF 100 mcg ranged between 36 mL and 89 mL at week 12; 193 mL between FF/VI 200/25 mcg and FF 200 mcg at week 24; and 210 mL between FF/VI 200/25 mcg and FP 500 mcg. These associations were consistent between evening trough FEV_1 and weighted mean serial FEV_1 within each study. Whether the improvements between FF/VI and monotherapy in evening trough and weighted mean serial FEV_1 are clinically meaningful remains unknown. However, there is some uncertainty regarding the robustness of these findings on lung function. For instance, in study HZA-829, a sensitivity analysis was conducted to remove one study site due to concerns about whether good clinical practice was adhered to. The treatment difference on weighted mean FEV_1 was no longer statistically significant ($P = 0.230$); similarly, subgroup analysis in the PP population was also no longer significant for this end point. It may be that, by removing these patients, the power was reduced for these analyses.

QoL measures can provide a complete picture of the improvements in key patient-identified outcomes such as pulmonary function, exacerbations, satisfaction with health, and impact of symptoms on daily function. Furthermore, patients with asthma have expressed a desire for new treatments to improve QoL (0). At both weeks 12 and 24, results of the AQLQ showed that, with the exception of the combination therapy comparator trial (HZA-091), the treatment groups in all other studies — including the placebo arm — achieved a mean change from baseline of more than 0.5 points, representing a clinically meaningful change from baseline values. No statistically significant differences emerged between the active treatment monotherapy and combination therapy comparators. The clinical expert consulted for this review noted that it is difficult to demonstrate differences in QoL between different treatments for asthma.

Few studies looked at the difference in resource consumption between different treatment groups and, overall, the reported average number of health care resource consumption was low across different sets of health care (≥ 0.1). According to the clinical expert consulted for this review, this is expected given that patients with asthma typically only seek health care resources when an exacerbation occurs, and in the trials that collected resource consumption, these patients were at lower risk of a severe exacerbation.

In the absence of adequate head-to-head trial data for FF/VI compared with other combination therapies, and given that a limited number of outcomes were studied in the manufacturer-sponsored study, HZA-091, an indirect treatment comparison (IDC) was conducted based on a systematic review of RCTs to compare the efficacy of FF/VI against other single-inhaler, fixed-dose combination therapies for asthma. The manufacturer's interpretation of the IDC was that FF/VI would be broadly similar to other ICS/LABA combination therapies across outcomes of PEF, FEV_1, AQLQ, and rates of moderate or severe exacerbation. However, given considerable concerns related to the reporting and conduct of the analysis, there is a high degree of uncertainty associated with the findings of the network meta-analysis (NMA) that was conducted.

In the manufacturer's submission to CDR, claims were made that: the Ellipta inhaler is "preferred by patients over other inhalers," and that its once-daily administration can improve adherence over twice-daily dosing. However, no strong evidence was found to substantiate either of these claims. One of the main studies cited by the manufacturer was conducted to evaluate patient preference for the Ellipta

device compared with Breezhaler (an inhaler not presently used in patients with asthma) among Japanese patients with COPD who were aged 40 years or older.[40] This was a non-drug crossover study in which patients were randomized to handle either the Ellipta or Breezhaler DPI until point of inhalation without verbal or demonstrative instruction, then crossed over to the other inhaler. The generalizability of this evidence to Canadian asthmatics is highly uncertain.

Furthermore, as an open-label study with patient-reported outcomes, the potential for bias to be introduced is likely considerable. A mixed-method study claimed that among 33 patients with asthma who had participated in either an FF/VI or FF dummy-designed trial, 71% (n = 15/21) preferred the Ellipta inhaler over the Diskus/Accuhaler, while 60% (n = 6/10) preferred Ellipta to the metered dose inhaler.[41] This represents a small sample size based on a convenience sample of 3% of the original trial population (i.e., total population originally enrolled: 238 and 847 patients in studies FFA-496 and HZA-827, respectively). This study further aimed to identify the key attributes to explain inhaler preferences. It is important to note that the themes identified are specific to a rather limited study sample and caution is warranted in generalizing these themes to a broader population, given concerns regarding statistical representation.[41]

Lastly, a conference abstract of an open-label randomized crossover trial has made claims that 81.2% (n = 121/149) of patients identified Ellipta as the easiest inhaler to operate when compared with Diskus/Accuhaler or TurbuHaler.[42] However, the generalizability of this study is uncertain given that this study was conducted on Japanese adults with no previous history of regular dry powder inhaler use, and the source information is limited to an abstract.[42] The clinical trial program for FF/VI further does not provide evidence to support the manufacturer's claim of better adherence. Indeed, adherence rates were similar in the double-dummy trials that evaluated both the Ellipta and Diskus/Accuhaler inhalers.

4.2.2 Harms

The incidence of AEs in patients treated with FF/VI was similar to those treated with monotherapy (FF, FP) and combination therapy (FP/S). SAEs were rare (< 7% across studies), and did not suggest any association with specific treatments. Three deaths were recorded during study HZA-837: two during the double-blind period; one in each treatment group; and one in the post-treatment follow-up in the FF group. They were all considered non–asthma related.

The most common AEs reported in any treatment group and across all studies were headache, upper respiratory tract infection, and nasopharyngitis. On-treatment infections and infestations were frequent, ranging from 11% to 46%, but were similar across treatment groups within each study.

Harms were not analyzed in the IDC and, with the exception of one study that directly compared FF/VI to FP/S, the comparative safety of FF/V versus other commonly prescribed, fixed-dose, single-inhaler combination therapies (e.g., budesonide/formoterol fumarate dihydrate [BUD/F] and mometasone furoate/formoterol fumarate dihydrate [MOM/F]) is unknown. Long-term (> 52 weeks) safety data for FF/VI are presently unavailable.

4.3 Potential Place in Therapy

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

Breo Ellipta is the fourth single-inhaler combination therapy of an ICS and LABA to be approved by Health Canada for chronic asthma. These combination inhalers are indicated for patients with diagnosed asthma[2,6] who are not successfully controlled by an ICS (at least at a low dose) along with the occasional use of a rapid onset SABA. FF/VI has overall demonstrated efficacy versus placebo and ICS alone in this population, with statistically significant improvements in lung function and reduced exacerbations. After asthma diagnosis, identification of patients with uncontrolled asthma is based mostly in general practice on symptoms and the frequency of SABA use.

The direct and indirect evidence for the comparative benefit of FF/VI versus other ICS/LABA combinations is limited. The manufacturer has also submitted some literature showing that a once-daily ICS increases adherence in patients with asthma when compared with a twice-daily ICS.[7] However, the differences expected in a clinical setting are likely small, and there is no direct evidence that once-daily therapy with FF/VI confers a clinically significant advantage over other ICS/LABA combination inhalers with twice-daily administration in patients with uncontrolled asthma. FF/VI is available in two doses (i.e., moderate and high doses of the ICS component based on equivalent FP); thus, it does not seem to cover the lower-dose ICS. Guidelines for the management of asthma, based on evidence from systematic reviews and RCTs, recommend that patients aged 12 years and older who are not achieving asthma control on a low dose of ICS benefit more from combination therapy with LABA than from increasing the maintenance dose of ICS.[2] Therefore, there is uncertainty as to the place in therapy for FF/VI when switching these patients, given that there may not be a want or need to increase to an equivalent moderate dose of ICS (i.e., the FF 100 mcg component). In addition, FF/VI cannot be used as both maintenance and rescue medication, unlike certain other ICS/LABA combinations, such as BUD/F.[2,6]

5. CONCLUSIONS

This analysis included seven double-blind RCTs that recruited patients ≥ 12 years of age with asthma who were inadequately controlled on ICS therapy, in which one or both dosages of FF/VI were compared against equivalent moderate- or high-dose ICS monotherapies (i.e., FF, FP), ICS/LABA combination therapy (i.e., FP/S), or placebo for a minimum of 12 weeks and up to a maximum of 76 weeks. There is very limited comparative evidence for FF/VI versus alternative ICS/LABA combination therapies. FF/VI was not statistically significantly superior to FP/S with respect to lung function. An NMA was provided by the manufacturer comparing FF/VI with the other ICS/LABA combination products; however, given the number of methodological and reporting issues present, the validity of the findings is highly uncertain. Therefore, the results show unclear comparative clinical benefit of FF/VI against other combination therapies.

Overall, FF/VI was statistically significantly superior to ICS monotherapy in reducing exacerbations among patients at higher risk for exacerbations, and for improving lung function (FEV_1 and PEF), although the evidence base was not considered robust and was of uncertain clinical significance. There was very little evidence to compare the effects of two doses of FF/VI on relevant outcomes. Also, the moderate to high doses of ICS used in the studies means that caution should be used when extrapolating the findings to patients uncontrolled on low-dose ICS. Moreover, there was no clear evidence for improved HRQoL or treatment adherence; there was limited evidence of uncertain clinical significance with respect to symptom improvement; and there was no evidence of reduction in health care resource use or days of missed work or school.

FF/VI appears to have a similar harms profile to the other ICS/LABA comparators, although longer-term comparative studies are needed to elucidate the harms of FF/VI beyond 52 weeks of exposure.

APPENDIX 1: PATIENT INPUT SUMMARY

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

1. Brief Description of Patient Group(s) Supplying Input
Two patient groups submitted input: the Ontario Lung Association (OLA) and the British Columbia Lung Association (BCLA).

The OLA is a charitable organization that assists and empowers people living with or caring for others with lung disease, including asthma. The association works closely with nine other provincial lung associations and the Canadian Lung Association. It reports receiving sponsorships and grants from a number of pharmaceutical companies, including Pfizer, GlaxoSmithKline, Boehringer Ingelheim, AstraZeneca, Merck, Novartis, J&J, Roche, Rx&D, and Eli Lilly, as well as the Ontario Home Respiratory Services Association, to support educational and research initiatives.

The BCLA is a charitable organization whose mission is to improve lung health and to lead lung health initiatives. Its areas of interest and expertise include the entire scope of respiratory diseases. It works together with the Canadian Lung Association and other partners to help people with breathing disorders. It reports receiving unrestricted educational grants from a number of pharmaceutical companies, including AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck Frosst, Novartis, Pfizer, and Grifols.

Both the OLA and BCLA have declared no conflict of interest in the preparation of their submissions.

2. Condition-Related Information
According to the OLA, the following information is based on five online surveys completed by people living with asthma and input from a certified respiratory educator. There was no information reported on the number of patients who completed the surveys, nor their demographics.

The BCLA did not explicitly identify the source(s) of information used to complete its patient input submission. It noted, however, that information on the drug being reviewed (Section 4) was based on knowledge and experience garnered through research, best practice guidelines, and direct involvement with patients alongside several support group meetings that involved patients with asthma in British Columbia.

Common challenges and symptoms of asthma reported by members of both patient groups included shortness of breath, chronic cough, wheezing, and impact on physical activities. The OLA also stated that fatigue, difficulty fighting infections, and management of weight loss were important challenges for people with asthma. The association also noted the extent to which asthma affects simple day-to-day activities, such as work.

Further, both groups commented on the negative impact of asthma on travel and family life. A respondent from the OLA commented on the negative effects of asthma on leisure, as follows:

> "*I cannot play more intensive sports, such as soccer and hockey*."

The BCLA echoed this, noting the compromise with leisure activities as well as the frustration and depression that may arise as a result of being restricted from everyday activities. It also highlighted the

major impact of the patient's compromised independence on caregivers. The OLA did not provide any information regarding the impact of asthma on patients' caregivers.

3. Current Therapy-Related Information

Respondents from the OLA noted that current treatments — e.g., Symbicort, Ventolin, and Alvesco with salbutamol — do provide some relief from symptoms, including fatigue, shortness of breath, cough, low energy, poor appetite, and the inability to fight infection. However, they report several adverse events (AEs) associated with current treatments, including hoarse voice, increased mucus, low energy or fatigue, appetite loss, and an impact on mood. They also acknowledged the cost burden of current treatments, as well as the intensive time requirements with regard to medical appointments.

The BCLA highlighted an unmet need related to existing asthma medication. In particular, there is an importance for medicines that will halt the progression of asthma, as well as prevent (or reduce) associated hospitalizations. It reported the need for therapies that will improve overall lung function and treat asthma as the disease progresses. Similarly, patients interviewed by the OLA reiterated that an ideal treatment would improve quality of life (QoL) and improve lung function. Additional outcomes they wished treatment could address included greater assistance with asthma management, such as reducing shortness of breath, coughing and fatigue; improving energy levels and appetite; and increasing the ability to fight infections.

4. Expectations About the Drug Being Reviewed

Only one patient from the OLA reported having experience with Breo Ellipta, and indicated reduced coughing while on treatment. Relative to other treatments, however, the patient rated Breo Ellipta as "worse than" other options in the areas of drug administration, side effects, and cost burden.

Respondents from the BCLA have had no experience using the drugs, although they noted that Breo Ellipta would be a new medication to try, as other medications often do not work for them. They expected that Breo Ellipta, when effective, would improve QoL. Patients with asthma and allergies who were interviewed said they understand that while there is no cure for their condition, they expect the new drug to slow the progression of their asthma and relieve symptoms. One patient described it as "buying time."

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	September 8, 2015
Alerts:	Bi-weekly search updates until January 13, 2016
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

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

MULTI-DATABASE STRATEGY	
Line #	**Search strategy**
1	((GW 642444* or GW642444* or UNII028LZY775B or 028LZY775B or vilanterol* or trifenatate* or 503068-34-6) and (GSK 685 698* or GSK 685698* or GW 685698* or GW 685 698* or JS86977WNV or UNIIJS86977WNV or 397864-44-7 or fluticasone furoate* or dluticasone furoate*)).ti,ab,sh,hw,ot,rn,nm,kw.
2	(Breo Ellipta* or revinity ellipta* or relvar ellipta* or (FF adj2 VI)).ti,ab,sh,hw,ot,kw.
3	(fluticasone furoate* adj3 (oral* or inhal* or ellipta* or powder*)).ti,ab,sh,hw,ot,kw.
4	S900006200.rn,nm.
5	1 or 2 or 3 or 4
6	5 use pmez

MULTI-DATABASE STRATEGY	
Line #	**Search strategy**
7	*fluticasone furoate plus vilanterol/
8	*fluticasone furoate/ and *vilanterol/
9	((GW 642444* or GW642444* or UNII028LZY775B or UNII 028LZY775B or vilanterol* or trifenatate* or 503068-34-6) and (GSK 685 698* or GSK 685698* or GW 685698* or GW 685 698* or UNII JS86977WNV or UNIIJS86977WNV or 397864-44-7 or fluticasone furoate or dluticasone furoate)).ti,ab.
10	(Breo Ellipta* or revinity ellipta* or relvar ellipta* or (FF adj2 VI)).ti,ab.
11	(fluticasone furoate* adj3 (oral* or inhal* or ellipta*)).ti,ab.
12	7 or 8 or 9 or 10 or 11
13	12 use oemezd
14	conference abstract.pt.
15	13 not 14
16	6 or 15
17	remove duplicates from 16

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	Search to August 2015
Keywords:	Breo Ellipta; Fluticasone furoate and vilanterol; asthma
Limits:	No date or language limits used

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

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

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Allen A, Schenkenberger I, Trivedi R, Cole J, Hicks W, Gul N, et al. Inhaled fluticasone furoate/vilanterol does not affect hypothalamic-pituitary-adrenal axis function in adolescent and adult asthma: randomized, double-blind, placebo-controlled study. Clin Respir J. 2013 Oct;7(4):397-406.[43]	Inappropriate comparator
Kempsford RD, Oliver A, Bal J, Tombs L, Quinn D. The efficacy of once-daily fluticasone furoate/vilanterol in asthma is comparable with morning or evening dosing. Respir Med. 2013 Dec;107(12):1873-80.[44]	Inappropriate comparator
Oliver A, Quinn D, Goldfrad C, van HB, Ayer J, Boyce M. Combined fluticasone furoate/vilanterol reduces decline in lung function following inhaled allergen 23 h after dosing in adult asthma: a randomized, controlled trial. Clin Transl Allergy. 2012;2(1):11.[45]	Phase 2 trial
Oliver A, Bjermer L, Quinn D, Saggu P, Thomas P, Yarnall K, et al. Modulation of allergen-induced bronchoconstriction by fluticasone furoate and vilanterol alone or in combination. Allergy. 2013 Sep;68(9):1136-42[46]	Phase 2 trial
Lotvall J, Bateman ED, Busse WW, O'Byrne PM, Woodcock A, Toler WT, et al. Comparison of vilanterol, a novel long-acting beta2-agonist, with placebo and a salmeterol reference arm in asthma uncontrolled by inhaled corticosteroids. J Negat Results Biomed. 2014;13(1).[47]	Use of non-approved dosage
Hussar DA, Ahmad A. Vilanterol trifenatate/fluticasone furoate, lomitapide mesylate, and mipomersen sodium. J Am Pharm Assoc (2003). 2013 Nov;53(6):662-70.[48]	Not a primary study

APPENDIX 4: VALIDITY OF OUTCOME MEASURES

Aim

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

- Forced expiratory volume in one second (FEV_1)
- Peak expiratory flow (PEF)
- Asthma Control Test (ACT)
- Asthma Quality of Life Questionnaire for 12 years and older (AQLQ +12)

Findings

The above outcome measures are briefly summarized in Table 32.

TABLE 32: VALIDITY AND MINIMAL CLINICALLY IMPORTANT DIFFERENCE OF OUTCOME MEASURES

Instrument	Type	Evidence of Validity	MCID (or Similar Parameter)	References
FEV_1	FEV_1 is the volume of air that can be forcibly exhaled in 1 second after a full inspiration.	Yes	MPPI: 10.4% change from baseline	None
PEF	PEF is the maximum flow rate achieved during a maximal forceful exhalation starting from full lung inflation.	Yes	MPPI: 18.8 L/min	None
ACT	ACT is a patient-reported tool to assess asthma control among adolescents and adults, i.e., aged ≥ 12 years. It consists of 5 items relating to different aspects of asthma control that patients are asked to recall from the previous 4 weeks. Each item is scored on a 5-point scale ranging from 1 to 5, with higher scores indicating better asthma control. Scores from individual items are added together to produce an overall score that ranges from 5 to 25.	Yes	3	Schatz et al., 2009[36]
AQLQ +12	AQLQ +12 is a patient-reported assessment of functional impairments experienced by individuals with asthma aged 12 years and older. It includes 32 questions grouped into 4 domains: (1) symptoms; (2) activity limitations; (3) emotional function; and (4) environmental stimuli. Each question is scored on a 7-point Likert scale, which ranges from 7 (no impairment) to 1 (severe impairment). The overall score is calculated as the mean of all questions, and the 4 domain scores are the means of the scores to the questions in the respective domains.	Yes	Unknown	None

ACT= Asthma Control Test; AQLQ +12= Asthma Quality of Life Questionnaire for 12 years and older; FEV_1 = forced expiratory volume in 1 second; MCID = minimal clinically important difference; min = minute; MPPI = minimal patient perceivable improvement; PEF = peak expiratory flow.

Forced Expiratory Volume in One Second

FEV_1 is the maximal amount of air forcefully exhaled in one second. The measured volume can be converted to a percentage of predicted normal value, which is adjusted based on height, weight, and race. The percentage of predicted FEV_1 is one of the most commonly reported pulmonary function tests.[37] Considered an acceptable primary end point (although recommended as a secondary clinical end point) by Health Canada,[49] FEV_1 is widely used in clinical trials to evaluate the effectiveness of asthma treatments.

Clinically, the percentage of predicted FEV_1 appears to be a valid marker for the degree of airway obstruction with asthma and other respiratory conditions, including chronic obstructive pulmonary disease and cystic fibrosis. Together with asthma symptoms and the use of inhaled short-acting beta2-agonists, FEV_1 is used to classify the severity of asthma.[50,51] There seems to be uncertainty, however, regarding the extent to which FEV_1 values are associated with quality of life (QoL), as researchers have reported variable correlations — ranging from none to strong[52-55] — among adults and children with asthma. However, FEV_1 values appear to correlate well with final clinical outcomes, such as the likelihood of hospitalization.[56] Further, FEV_1 values demonstrate high within-session repeatability: in a study of 18,526 adult patients, of whom 11% gave a history of physician-diagnosed asthma, 90% were able to reproduce FEV_1 within 120 mL.[57]

There appears to be limited evidence of an MCID for FEV_1 among individuals with asthma. In one study of 281 adult asthmatic patients (baseline mean FEV_1 2.30 ± 0.66 L/s), researchers calculated the minimal patient perceivable improvement (MPPI) for FEV_1 by comparing the average scores from baseline for FEV_1 against patient global ratings of change in asthma. Across all patients, the MPPI for FEV_1 was 230 mL, or 10.38% change from baseline. Males and females showed similar MPPI values, but older patients had a lower MPPI (170 mL) than younger individuals (280 mL) for FEV_1.[58]

Peak Expiratory Flow

PEF — sometimes referred to as peak expiratory flow rate (PEFR) — is defined as "the maximum flow achieved during an expiration delivered with maximal force starting from the level of maximal lung inflation."[38] It can be measured using a mechanical peak flow meter, in which case patients may be asked to record the PEF values in diaries. There is strong evidence, however, that these diaries are often unreliable among asthmatic patients, particularly children.[59-61] Alternatively, PEF may be measured using electronic peak flow metres, which automatically store and download measurements as needed. PEF is usually expressed in units of litres per minute (L/min), and sometimes as a percentage of the predicted normal value or as a change from baseline average values.[62]

PEF values appear to discriminate between patients with reversible and irreversible airflow obstruction.[63] PEF values also appear to be valid clinical markers of airway responsiveness and asthma severity.[62] In addition, they seem to correlate well with other measures of lung function, including FEV_1,[64] although there appears to be a paucity of evidence directly linking PEF with QoL.

Some trialists have used a value of 25 L/min as an MCID for PEF values among patients with asthma.[65,66] No research, however, seems to support the use of this cut point. In one study of 281 adult asthmatic patients, researchers calculated the MPPI for PEF by comparing the average scores from baseline for PEF against patient global ratings of change in asthma. Across all patients, the MPPI for PEF was 18.8 L/min, with no differences in MPPI values by gender or age.[58] In another study, researchers noted a predicted PEFR of about 12% to be a minimal clinically significant improvement among patients presenting to the emergency department with acute asthma exacerbation.[67]

Asthma Control Test

The ACT is a patient-reported tool to assess asthma control among adolescents and adults; i.e., aged 12 years and older. Developers of the ACT originally convened a working group, which included primary care clinicians and asthma specialists from the United States, to develop a list of 22 items that reflected the multi-dimensional nature of asthma control.[35] The researchers then recruited patients with asthma to complete the 22-item survey, and used stepwise logistic regression analyses to identify the items with the greatest validity in discriminating between patients who differed in their specialists' ratings of asthma control.[35] Based on their analyses, the investigators chose the following five items for inclusion in the ACT: (1) shortness of breath; (2) patient's rating of asthma control; (3) use of rescue medication; (4) role limitations due to asthma; and (5) nocturnal asthma symptoms.[35] Each item is scored on a 5-point scale ranging from 1 to 5, with greater scores indicating better asthma control. Scores from the individual items are added together to produce an overall score that ranges from 5 to 25.[35] Patients recall their relevant experiences during the previous four weeks.

The ACT was originally validated in a cross-sectional study of patients (n = 471) with asthma who were under the routine care of an asthma specialist.[35] In this study, researchers noted low and moderate correlation between the ACT and FEV_1 (r = 0.19; P = 0.0001) and specialists' ratings of asthma control (r = 0.45; P = 0.0001), respectively. The internal consistency reliability of the ACT was 0.84. The researchers noted that ACT scores discriminated between groups of patients who differed in their specialists' ratings of asthma control, the need for change in their therapy (i.e., step down, no change, step up in therapy), and their percentage predicted FEV_1 values. A cut point of 19/25 demonstrated the highest area under the receiver operating characteristic (ROC) curve (0.727); the overall agreement between the ACT and the specialist's rating was 74.1% at this cut point.

Researchers have also validated the ACT in patients not previously followed by asthma specialists,[68] as well as a version administered over the Internet,[69] the telephone,[70] and in home settings.[71] A systematic review of 21 studies (enrolling 11,141 patients) concluded that the ACT had good diagnostic accuracy for the assessment of controlled and not well-controlled asthma: pooled sensitivity and specificity values at levels of controlled and not well-controlled asthma were 0.77 (95% CI, 0.68 to 0.84) and 0.84 (95% CI, 0.74 to 0.91), 0.75 (95% CI, 0.63 to 0.83) and 0.82 (95% CI, 0.76 to 0.87), respectively.[72] The study investigators, however, concluded poor accuracy of the ACT for the assessment of uncontrolled asthma: pooled sensitivity and specificity values of 0.49 (95% CI, 0.42 to 0.56) and 0.92 (95% CI, 0.86 to 0.96), respectively; and a hierarchical summary ROC area under the curve (AUC) of 0.69.[72]

In a study involving four independent samples of adults (n = 4,018) with asthma, researchers used a variety of distribution- and anchor-based methods to establish the MCID for the ACT.[36] In particular, their anchor-based methods assessed the relationship between mean ACT scores and the following items: (1) patient's self-report of asthma severity; (2) patient's self-report of number of asthma episodes; (3) spirometry values; (4) specialist global assessment; (5) specialist-recommended change in therapy; (6) patient self-report of change in asthma; (7) short-acting beta-agonist dispensing more than six canisters; and (8) asthma exacerbations. Based on their analyses, the authors proposed an MCID of three units for the ACT.[36]

Asthma Quality of Life Questionnaire for 12 Years and Older

The AQLQ +12 is a patient-reported, disease-specific, health-related quality of life (HRQoL) measure that is a variant of the standardized version of the AQLQ (AQLQ[S]) developed by Juniper et al.[31] To accommodate the larger group of patients with asthma in whom the instrument is intended to be used, i.e., 12 years and older versus adults only, the developers of AQLQ(S) altered one question about "work-

related limitations" to "work-/school-related limitations."[32] As with the original questionnaire, the AQLQ +12 includes 32 questions grouped into four domains: (1) symptoms; (2) activity limitations; (3) emotional function; and (4) environmental stimuli. Each question is scored on a 7-point scale, which ranges from 7 (no impairment) to 1 (severe impairment). The overall score is calculated as the mean of all questions, and the four domain scores are the means of the scores for the questions in the respective domains. Patients recall their relevant experiences during the previous two weeks.

Overall, the AQLQ +12 showed high internal consistency at baseline: a Cronbach alpha > 0.90, dependent on the age group; i.e., 12 to 17 years or ≥ 18 years.[33,73] The AQLQ +12 was originally validated in a secondary analysis of two clinical trials, which included 2,433 patients with asthma (baseline mean FEV_1 % predicted [range] ≥ 18 years: 75.4 [32 to 136] and 73.3 [41 to 107]; 12 to 17 years: 83.9 [47 to 125] and 77.8 [54 to 114] in trials 1 and 2, respectively).[32] The cross-sectional (baseline) and longitudinal (baseline to end of study) construct validity between AQLQ +12 and other measures of asthma clinical status — including FEV_1 percentage of predicted value, PEF, symptoms, night walking, and amount of rescue medication — was variable, with Pearson correlation coefficients indicating none to moderate associations. In a subsequent pooled analysis conducted by another group of researchers, however, the AQLQ +12 demonstrated excellent overall test–retest reliability (intraclass correlation coefficient [ICC]) of 0.86 in one study and 0.83 in the other); moderate to strong construct validity with other indices of asthma (i.e., baseline Asthma Control Questionnaire score and mean daytime and nighttime symptom diary-scale scores); strong known-groups validity; and excellent responsiveness.[33] No study appears to have formally established the MCID for AQLQ +12; however, given the significant overlap between the AQLQ +12 and the original AQLQ, researchers consider a cut point of 0.5 to indicate a clinically important difference, given that this is the MCID for AQLQ(S).[32-34]

Conclusion

Overall, FEV_1, PEF, ACT, and AQLQ +12 appear to be validated outcomes for use in clinical trials of therapies for patients with asthma. Only the ACT, however, seems to have a rigorously established MCID of 3. A review of the literature did not find an MCID for the other outcomes.

APPENDIX 5: SUMMARY OF INDIRECT COMPARISONS

1. Introduction

1.1 Background

There is limited direct evidence on the efficacy of fluticasone furoate/vilanterol (FF/VI) versus existing combination therapies, as the manufacturer submitted only one study that evaluated FF/VI 100/25 mcg versus fluticasone propionate/salmeterol (FP/S) 250/50 mg.

The aim of this section is to identify, summarize, and critically appraise indirect comparisons (IDCs) that provide evidence for the efficacy and harms of FF/VI 100/25 mcg once daily and 200/25 mcg once daily versus other combination therapies for the maintenance treatment of asthma.

1.2 Methods

An information specialist conducted a systematic literature search to identify published IDCs. The details of the literature search are available in APPENDIX 2.

2. Description of Indirect Comparisons Identified

One IDC was submitted by the manufacturer. No published IDCs were identified in the literature search.

3. Review and Appraisal of Indirect Comparisons

3.1 Review of Manufacturer's Indirect Comparison

3.1.1 Objectives and Rationale for Manufacturer's Indirect Comparison

The primary objective of the manufacturer's IDC was to evaluate the efficacy of FF/VI 100/25 mcg and FF/VI 200/25 mcg once daily versus other medium- and high-dose inhaled corticosteroid/long-acting beta2-agonist (ICS/LABA) fixed-dose combination products for the maintenance treatment of asthma among adolescents and adults; i.e., aged 12 years and older.

3.2 Methods for Manufacturer's Indirect Comparison

3.2.1 Study Eligibility and Selection Process

a) Literature Search

Studies were included in the IDC if they were published in English and identified by searches on Embase, MEDLINE, MEDLINE In-Process, or the Cochrane Central Register of Controlled Trials, from the inception of each database to December 18, 2012.

In addition, abstracts from conference proceedings published from 2010 to 2012 by three groups — the European Respiratory Society, the American Thoracic Society, and the American College of Chest Physicians (CHEST) — were included. Bibliographies of systematic reviews, clinical controlled trials websites, the US Food and Drug Administration website, and the European Medicines Agency website were searched for eligible studies for inclusion.

Finally, six manufacturer-sponsored study reports that evaluated the efficacy of FF/VI for asthma were included.

b) Eligibility Criteria

Studies were eligible for inclusion that were phase 3 or phase 4 parallel-group randomized controlled trials (RCTs), irrespective of blinding status; enrolled adolescents and adults (aged ≥ 12 years) with

uncontrolled or symptomatic asthma, irrespective of gender, race, or severity of illness, and who were on ICS or ICS/LABA at randomization; and were longer than eight weeks in duration.

A key exclusion criterion was trials that contained at least one study arm that included flexible dosing or that studied a range of doses.

Study Selection
Two reviewers independently screened citation titles and abstracts and selected full-text published articles based on predefined eligibility criteria. At each stage, a third, independent reviewer resolved any discrepancies that arose between reviewers.

Data Extraction
Two independent reviewers conducted data extraction. A third, independent reviewer resolved any discrepancies.

Comparators
Comparators of interest were any active treatments for asthma, including:
- ICS
- LABA
- Long-acting muscarinic antagonists (LAMA)
- Any dual combination therapy (ICS/LABA, ICS/LAMA, LABA/LAMA) in combined or separate inhalers
- Any triple combination (ICS/LABA/LAMA)

Placebo and supportive care were also included as relevant comparators. Key medium-dose ICS/LABA comparators for FF/VI 100/25 mcg that the manufacturer included were:
- FP/S 250/50 mcg twice daily
- Budesonide/formoterol fumarate dihydrate (BUD/F) 400/12 mcg twice daily
- Beclomethasone dipropionate (extra-fine)/formoterol fumarate dihydrate (BDP [extra-fine]/F) 200/12 mcg twice daily
- FP/F 250/10 mcg twice daily
- Mometasone furoate/formoterol fumarate dihydrate (MOM/F) 200/10 mcg twice daily

Key high-dose ICS/LABA comparators for FF/VI 200/25 mcg that the manufacturer included were:
- FP/S 500/50 mcg twice daily
- BUD/F 800/24 mcg twice daily
- FP/F 500/20 mcg twice daily
- MOM/F 400/10 mcg twice daily

Different doses of the same drug were analyzed separately in the network. Treatment arms were grouped together only if they delivered the same dose per administration, irrespective of the number of puffs per administration, and the same number of administrations per day, irrespective of the device. Based on discussions with the clinical expert involved in this review, however, BDP (extra-fine)/F and FP/F are less relevant comparators because they are not commonly used in Canadian clinical practice. Thus, this summary was restricted to comparing the efficacy of FF/VI against the other Health Canada–approved fixed-dose, single-inhaler ICS/LABA combination products only; i.e., FP/S, BUD/F, and MOM/F.

Outcomes
The following efficacy outcomes were included in the IDC:

1. Mean change from baseline in morning peak expiratory flow (PEF)

Morning PEF was analyzed based on mean change (in litres per minute [L/min]) from baseline to the end of the trial. One sensitivity analysis was conducted in which studies that did not report change in PEF from baseline to study end, but rather to an interim time point, were added.

2. Mean change from baseline in forced expiratory volume in one second (FEV_1)

FEV_1 was analyzed based on mean change (in mL) from baseline to the end of the trial. Included studies on FF/VI measured FEV_1 in the evening, while most other studies (with other comparators) assessed FEV_1 in the morning. The manufacturer prioritized extraction of trough FEV_1 and pre-bronchodilator values. If FEV_1 measures were unclear, it was assumed they were trough FEV_1 pre-bronchodilator and extracted accordingly. Additionally, when studies reported both morning and evening mean change in FEV_1 values, morning values were used.

No sensitivity analyses were conducted on this outcome.

3. Mean annual rates of moderate or severe exacerbation

Moderate or severe asthma exacerbations were defined as deterioration of asthma requiring:

- the use of systemic or oral corticosteroids (tablets, suspension, or injection) for at least three days, or
- an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids.

For the acute exacerbations analyses, studies had to report rate of exacerbations and the number of exacerbation events, or the number of exacerbation events and the patient-years of follow-up. The mean annual rates of moderate or severe exacerbation were used for the IDC analysis. Although trials did not need to have an identical definition to the above, studies were excluded if the definition encompassed symptom, rescue inhaler use, or lung-function changes alone. Studies were excluded from the analyses if they excluded patients with a history of exacerbations over a period longer than six months, and the definition of exacerbation differed considerably from the definition of a severe exacerbation used in the manufacturer's studies on FF/VI, or if patients were withdrawn after experiencing an exacerbation during the trial period.

Two sensitivity analyses were conducted in which alternate versions of the person-years calculations were used. Specifically, in these analyses, study participants lost to follow-up were assumed to have experienced 25% or 75% of the possible follow-up time versus the 50% follow-up that was assumed in the base-case analyses.

4. Mean change from baseline in Asthma Quality of Life Questionnaire (AQLQ) total score

Health-related quality of life (HRQoL) was assessed using mean change in AQLQ total score from baseline to the end of the trial. Scores from the standardized Asthma Quality of Life Questionnaire (AQLQ[S]) or the AQLQ for 12 years and older (AQLQ +12) were included because the scoring and interpretation of the instruments was considered to be the same for both instruments.

The authors did not conduct any sensitivity analyses for this outcome.

For each of the four outcomes, the authors conducted a secondary analysis of trials that enrolled patients who were only on ICS at randomization.

The authors did not evaluate the relative harms of FF/VI.

Quality Assessment of Included Studies

The authors used the CONSORT checklist to assess the reporting quality of each included study.

3.2 Indirect Comparison Methods

The manufacturer's IDC used a Bayesian hierarchical model to synthesize the data. Specifically, they constructed four models — one per clinical outcome of interest. The general mathematical structure of each model was as follows:

$$Y = Study + Treat + Covariate$$

The outcome variable (Y) represented the efficacy outcome of interest, while the model incorporated three sets of independent variables: study effects, treatment effects, and covariates.

Study effects were modelled using a random-effects approach, thus facilitating the creation of two levels (hierarchies) of analyses: within-study and between-study. Treatment effects were independently modelled using a fixed-effects approach; i.e., at the between-study level of the hierarchical model, although no rationale for this selection was provided.

A fixed-effects approach was also used to model the covariates, again with no rationale supporting the selection of this approach. According to the IDC protocol, the following covariates were considered for inclusion in the models: percentage of patients younger than 18 years; asthma severity at baseline; prior use of ICS; prior use of short-acting beta2-agonist; disease status; and reversibility of FEV_1 at baseline. Additionally, the protocol stated that an analysis of the impact of study duration on treatment effects may be explored. No rationale was provided for the selection of the covariates, or of their anticipated effects on treatment estimates. The final models included four covariates, of which one (length of study) was pre-specified, while the remaining three were not: mean age of participants at baseline; percentage of males in a treatment group; and mean baseline FEV_1 values. Each covariate was represented by a separate coefficient and normalized in the model; therefore, the base-case analysis represented a study that enrolled participants of a mean age of 40 years, with 40% males, average baseline FEV_1 of 2.4 L, and a study length of approximately one year.

The three continuous variables (change in PEF, FEV_1, and AQLQ) were analyzed using a normal distribution model, whereas a Poisson model was used to analyze the annual rate of exacerbations. No rationale was provided for the choice of distributions, nor did the IDC validate the assumptions. Non-informative priors were used for all parameters in the models.

The network also included disconnected treatments; i.e., those that were not linked via sequences of direct or IDCs. For example, if treatment A is exclusively compared against B and C, and treatment X is exclusively compared against Y and Z, because there is no link between treatments A and X, they would be considered disconnected. The authors relied on the magnitude of study-to-study variability (τ) to make inferences about the relative efficacy of disconnected treatments. The manufacturer assessed model fit by evaluating the plot of the residuals; i.e., the difference between the model estimated values and the observed values. The mixed treatment comparisons were performed using standard Markov

chain Monte Carlo methodology, and using adaptive Metropolis–Hastings steps as needed. Model results were reported using a single chain of length of 100,000 with a burn-in of 10,000.

The manufacturer did not explore for heterogeneity (clinical, methodological, or statistical) among the pairwise comparisons in the network; nor did they conduct formal tests of consistency — i.e., whether the direct evidence agreed with the indirect evidence.

3.2.1 Special Issues: Evaluation of Non-inferiority

One objective of the manufacturer's IDC was to evaluate the probability that FF/VI 100/25 mcg and FF/VI 200/25 mcg once daily are non-inferior to other medium- and high-dose ICS/LABA combination products. The Bayesian analytical framework described above was used to accomplish this objective. In some cases, multiple margins were specified in the report, although none were pre-specified in the protocol. The following margins were used to assess the extent to which FF/VI 100/25 mcg and FF/VI 200/25 mcg were non-inferior to other therapies for each outcome of interest:

- Morning PEF change of 12 L/min and 15 L/min from baseline. These thresholds were based on expert opinion and on margins used in previous trials, specifically citing four studies, of which two used a threshold of 15 L/min to demonstrate equivalence or non-inferiority. The authors did not specify whether any of the trials evaluated FF/VI 100/25 mcg or FF/VI 200/25 mcg.
- FEV_1 change of 75 mL, 100 mL, and 125 mL from baseline. These thresholds were based on margins used in previous manufacturer-sponsored trials — none of which evaluated FF/VI 100/25 mcg or FF/VI 200/25 mcg — and in a study that established a minimal clinically important difference (MCID) for this outcome.
- Exacerbation event rate ratios of 0.1 and 0.2. These thresholds were based on margins from one previous trial. The authors did not specify whether this trial evaluated FF/VI 100/25 mcg or FF/VI 200/25 mcg.
- AQLQ total score change of 0.25 and 0.5 from baseline. These thresholds were based on the MCID for the AQLQ, specifically using its full (0.5) and half (0.25) values.

3.3 Results

The manufacturer's IDC included 31 studies in its primary analyses. There was a total of 75 treatment groups that reflected 24 unique treatments.

Across the eligible trials, study participants were, on average, 41.74 years old and had a mean baseline FEV_1 of 2.3 L. Fewer than half (40.51%) were male. For the end point analyses, 18 studies reported change from baseline in PEF; 28 reported change from baseline in FEV_1; six reported annual rate of exacerbations; and seven reported change from baseline in AQLQ total scores.

3.3.1 Evidence Network

Five network graphs — one that illustrated all studies included in the systematic review, and four that represented studies specific to each outcome of interest — were generated and provided in the submission.

a) Change from Baseline in Peak Expiratory Flow

Studies Enrolling Patients on ICS and/or ICS/LABA at Randomization

Eighteen studies reported mean change from baseline in morning PEF.

In the full covariate model, when compared with other medium-dose ICS/LABA drugs, treatment with FF/VI 100/25 mcg was not associated with a statistically significant improvement in change from

baseline in morning PEF (Table 33). Treatment with FF/VI 200/50 mcg, however, was associated with a statistically significant improvement in change from baseline in morning PEF versus FP/S 500/50 mcg: mean difference of 11.323 (95% credible interval [CrI], 0.289 to 22.357). There were no data comparing FF/VI with MOM/F at both doses. The probability that FF/VI 100/25 mcg and FF/VI 200/25 mcg were non-inferior to other ICS/LABA drugs ranged from 0.94 to more than 0.99 (Table 33). Overall, these results were consistent with the estimates generated in the reduced (time covariate-only) model.

TABLE 33: RESULTS OF FULL COVARIATE MODEL FOR CHANGE FROM BASELINE MORNING PEF VALUES FOR FF/VI 100/25 MCG AND FF/VI 200/25 MCG VERSUS OTHER MEDIUM- AND HIGH-DOSE ICS/LABA AGENTS (FOR PATIENTS WITH ASTHMA WITH ICS OR ICS/LABA AT RANDOMIZATION)

Treatment (A)	Comparator (B)	Mean Difference (95% CrI)	Pr (A~B | 12 L/min)	Pr (A~B | 15 L/min)
FF/VI 100/25 mcg	FP/S 250/50 mcg	2.832 (–12.867 to 18.531)	0.97	0.99
FF/VI 100/25 mcg	BUD/F 400/12 mcg	0.579 (–15.155 to 16.312)	0.94	0.98
FF/VI 100/25 mcg	MOM/F 200/10 mcg	No data available		
FF/VI 200/25 mcg	**FP/S 500/50 mcg**	**11.323 (0.289, 22.357)**	**> 0.99**	**> 0.99**
FF/VI 200/25 mcg	BUD/F 800/24 mcg	15.136 (–0.943 to 31.215)	> 0.99	> 0.99
FF/VI 200/25 mcg	MOM/F 400/10 mcg	No data available		

BUD = budesonide; CrI = credible interval; F = formoterol fumarate dihydrate; FF = fluticasone furoate; FP = fluticasone propionate; ICS = inhale corticosteroid; LABA = long-acting beta2-agonist; min = minute; MOM = mometasone furoate; NMA = network meta-analysis; PEF = peak expiratory flow; Pr A~B = probability that treatment A is non-inferior to treatment B; S = salmeterol; VI = vilanterol.
Note: Bolded results indicate statistically significant findings.
Source: Manufacturer's NMA.[74]

Studies Enrolling Patients on ICSs Only at Randomization
The manufacturer did not exclude any studies for the ICS-only analysis. In other words, the ICS-only analysis would have been the same as the base-case analysis that was presented above.

Sensitivity Analyses
One sensitivity analysis was conducted in which nine studies were added that did not report change in PEF from baseline to study end, but rather to an interim time point. The results of these analyses were consistent with the primary analyses.

b) Change from Baseline in FEV_1
Studies Enrolling Patients on ICS and/or ICS/LABA at Randomization
Twenty-eight studies reported mean change from baseline in FEV_1.

In the full covariate model, when compared with medium-dose ICS/LABA drugs, treatment with FF/VI 100/25 mcg was not associated with a statistically significant improvement in change from baseline in FEV_1 (Table 34). Treatment with FF/VI 200/50 mcg, however, was associated with a statistically significant improvement in change from baseline in FEV_1 versus FP/S 500/50 mcg and MOM/F 400/10 mcg: mean difference of 0.147 (95% CrI, 0.048 to 0.247) and 0.186 (95% CrI, 0.027 to 0.346), respectively. The probability that FF/VI 100/25 mcg and FF/VI 200/25 mcg were non-inferior to other ICS/LABA drugs ranged from 0.91 to more than 0.99 (Table 34). Overall, these results were consistent with the estimates generated in the reduced (time covariate-only) model.

TABLE 34: RESULTS OF FULL COVARIATE MODEL FOR CHANGE FROM BASELINE FEV_1 VALUES FOR FF/VI 100/25 MCG AND FF/VI 200/25 MCG VERSUS OTHER MEDIUM- AND HIGH-DOSE ICS/LABA AGENTS (FOR PATIENTS WITH ASTHMA WITH ICS OR ICS/LABA AT RANDOMIZATION)

Treatment (A)	Comparator (B)	Mean Difference (95% CrI)	Pr (A~B | 75 mL)	Pr (A~B | 100 mL)	Pr (A~B | 125 mL)
FF/VI 100/25 mcg	FP/S 250/50 mcg	–0.036 (–0.092 to 0.019)	0.92	0.99	> 0.99
FF/VI 100/25 mcg	BUD/F 400/12 mcg	–0.027 (–0.098 to 0.045)	0.91	0.98	> 0.99
FF/VI 100/25 mcg	MOM/F 200/10 mcg	0.013 (–0.065 to 0.092)	0.99	> 0.99	> 0.99
FF/VI 200/25 mcg	**FP/S 500/50 mcg**	**0.147 (0.048 to 0.247)**	**> 0.99**	**> 0.99**	**> 0.99**
FF/VI 200/25 mcg	BUD/F 800/24 mcg	0.118 (–0.019 to 0.255)	> 0.99	> 0.99	> 0.99
FF/VI 200/25 mcg	**MOM/F 400/10 mcg**	**0.186 (0.027 to 0.346)**	**> 0.99**	**> 0.99**	**> 0.99**

BUD = budesonide; CrI = credible interval; F = formoterol fumarate dihydrate; FEV_1 = forced expiratory volume in one second; FF = fluticasone furoate; FP = fluticasone propionate; ICS = inhale corticosteroid; LABA = long-acting beta2-agonist; MOM = mometasone furoate; NMA = network meta-analysis; Pr A~B = probability that treatment A is non-inferior to treatment B; S = salmeterol; VI = vilanterol.
Note: Bolded results indicate statistically significant findings.
Source: Manufacturer's NMA.[74]

Studies Enrolling Patients on ICS Only at Randomization
Two studies from the ICS-only analysis were excluded. The results of this analysis were consistent with those generated in the primary analysis.

Sensitivity Analyses
The manufacturer did not conduct any sensitivity analyses for this outcome.

c) Annual Rate of Moderate or Severe Exacerbations
Studies Enrolling Patients on ICS and/or ICS/LABA at Randomization
Six studies reported annual rates of moderate or severe exacerbations.

Only the time covariate-only and no-covariate models converged for the analysis of this outcome. In the time covariate-only model, when compared with other medium-dose ICS/LABA drugs, treatment with FF/VI 100/25 mcg was not associated with a statistically significant reduction in the annual rate of moderate-to-severe exacerbations (Table 35). There were no data available comparing FF/VI 200/25 mcg with other high-dose ICS/LABA therapies relevant to this review. The probability that FF/VI 100/25 mcg was non-inferior to other medium-dose ICS/LABA drugs ranged from 0.74 to 0.86 (Table 35).

TABLE 35: RESULTS OF TIME COVARIATE-ONLY MODEL FOR CHANGE FROM BASELINE FEV1 VALUES FOR FF/VI 100/25 MCG AND FF/VI 200/25 MCG VERSUS OTHER MEDIUM- AND HIGH-DOSE ICS/LABA AGENTS (FOR PATIENTS WITH ASTHMA WITH ICS OR ICS/LABA AT RANDOMIZATION)

Treatment (A)	Comparator (B)	Event Rate Ratio A/B (95% CrI)	Pr (A~B | 0.10)	Pr (A~B | 0.20)
FF/VI 100/25 mcg	FP/S 250/50 mcg	1.164 (0.428 to 3.333)	0.74	0.78
FF/VI 100/25 mcg	BUD/F 400/12 mcg	0.985 (0.336 to 2.574)	0.82	0.86
FF/VI 100/25 mcg	MOM/F 200/10 mcg	No data available		
FF/VI 200/25 mcg	FP/S 500/50 mcg	No data available		
FF/VI 200/25 mcg	BUD/F 800/24 mcg	No data available		
FF/VI 200/25 mcg	MOM/F 400/10 mcg	No data available		

BUD = budesonide; CrI = credible interval; F = formoterol fumarate dihydrate; FEV_1 = forced expiratory volume in one second; FF = fluticasone furoate; FP = fluticasone propionate; ICS = inhale corticosteroid; LABA = long-acting beta2-agonist; MOM = mometasone furoate; NMA = network meta-analysis; Pr A~B = probability that treatment A is non-inferior to treatment B; S = salmeterol; VI = vilanterol.
Source: Manufacturer's NMA. [74]

Studies Enrolling Patients on ICS Only at Randomization
No studies were excluded from the ICS-only analysis.

Sensitivity Analyses
Two sensitivity analyses were conducted to assess alternate versions of the person-years calculations in order to estimate the number of person-years, when needed. The results of these analyses were consistent with the primary analyses.

d) Change from Baseline in AQLQ
Studies Enrolling Patients on ICS and/or ICS/LABA at Randomization
Seven studies reported mean change from baseline in AQLQ total scores.

In the full covariate model, when compared with other medium-dose ICS/LABA drugs, treatment with FF/VI 100/25 mcg was not associated with a statistically significant improvement in quality of life (QoL) (Table 36). There were no data available comparing FF/VI 200/25 mcg with the other high-dose ICS/LABA therapies in which this review was interested. The probability that FF/VI 100/25 mcg was non-inferior to other medium-dose ICS/LABA drugs ranged from 0.90 to more than 0.99 (Table 36). Overall, these results were consistent with the estimates generated in the reduced (time covariate-only) model.

TABLE 36: RESULTS OF FULL COVARIATE MODEL FOR CHANGE FROM BASELINE AQLQ VALUES FOR FF/VI 100/25 MCG AND FF/VI 200/25 MCG VERSUS OTHER MEDIUM- AND HIGH-DOSE ICS/LABA AGENTS (FOR PATIENTS WITH ASTHMA WITH ICS OR ICS/LABA AT RANDOMIZATION)

Treatment (A)	Comparator (B)	Mean Difference (95% CrI)	Pr (A~B | 0.25)	Pr (A~B | 0.5)
FF/VI 100/25 mcg	FP/S 250/50 mcg	0.060 (–0.104 to 0.224)	> 0.99	> 0.99
FF/VI 100/25 mcg	BUD/F 400/12 mcg	0.203 (–0.461 to 0.867)	0.90	0.96
FF/VI 100/25 mcg	MOM/F 200/10 mcg	No data available		
FF/VI 200/25 mcg	FP/S 500/50 mcg	No data available		
FF/VI 200/25 mcg	BUD/F 800/24 mcg	No data available		
FF/VI 200/25 mcg	MOM/F 400/10 mcg	No data available		

AQLQ = Asthma Quality of Life Questionnaire; BUD = budesonide; CrI = credible interval; F = formoterol fumarate dihydrate; FF = fluticasone furoate; FP = fluticasone propionate; ICS = inhale corticosteroid; LABA = long-acting beta2-agonist; MOM = mometasone furoate; NMA = network meta-analysis; Pr A~B = probability that treatment A is non-inferior to treatment B; S = salmeterol; VI = vilanterol.
Source: Manufacturer's NMA. [74]

Studies Enrolling Patients on ICS Only at Randomization
The manufacturer excluded one study from the ICS-only analysis. The results of this analysis were consistent with those generated in the primary analysis.

Sensitivity Analyses
The authors did not conduct any sensitivity analyses for this outcome.

3.3.1 Critical Appraisal

The IDC included studies that enrolled adolescents and adults — i.e., aged 12 years or older — with uncontrolled or symptomatic asthma, irrespective of gender, race, or severity of illness, and who were on ICS or ICS/LABA at randomization. However, the Health Canada–approved indication and the manufacturer's reimbursement listing request is for adults only — i.e., those aged ≥ 18 years; the IDC did not specifically evaluate the effectiveness of FF/VI 100/25 mcg and FF/VI 200/25 mcg in this population, nor did it conduct subgroup analyses to test for important differences in treatment effects between adolescents and adults. In addition, although it did not limit trials by participants' gender, race, or severity of illness, the manufacturer provided limited information on the baseline characteristics of patients enrolled in the eligible trials, which makes the generalizability of its findings to the Canadian setting uncertain.

A wide range of comparators were included, many of which are relevant in the Canadian setting, including FP/S (Advair), BUD/F (Symbicort), and MOM/F (Zenhale). The IDC, however, also included ICS/LABA drugs that were less relevant to the Canadian market — i.e., BDP (extra-fine)/F and FP/F — which limits the generalizability of the results.

The analysis included certain clinically relevant efficacy outcomes, but it did not evaluate the relative harms of FF/VI 100/25 mcg and FF/VI 200/25 mcg; therefore, the comparative safety of FF/VI versus other ICS/LABA combinations remains uncertain.

Although it was reported that multiple databases were searched for eligible trials for inclusion, search strategies were not provided, and the CDR reviewers were unable to assess the comprehensiveness of

the searches. It was reported that screening of studies for eligibility occurred over multiple phases (titles or abstracts and full-texts) by two reviewers working independently, with third-party adjudication as needed. However, the level of agreement between reviewers for the selection of eligible articles was not reported, which leaves the reproducibility of the study selection uncertain. While the manufacturer did assess reporting quality for the individual studies, it did not assess risk of bias, hence limiting our ability to evaluate the internal validity of the included studies, and ultimately judge the underlying quality of the evidence.

The manufacturer included trials that enrolled patients who were on ICS or ICS/LABA at randomization. Rather than conducting formal tests of interactions to assess whether treatment effects significantly differed across the ICS-only and ICS/LABA subgroups, the manufacturer analyzed each population separately, which leaves the credibility of its analyses uncertain, as we cannot exclude the possibility that any differences in treatment effects may be due to chance.[75]

Further, a sensitivity analysis was conducted in which nine studies were added that did not report change in PEF from baseline to study end, but rather to a specific time point. No information was provided regarding the extent to which the time points were similar across the studies, which raises concerns about heterogeneity.

The hierarchical models used in the analysis incorporated four covariates, which may have helped adjust for imbalances in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials. A key issue, however, is that only one of them (length of study) was pre-specified, and five of the six pre-specified covariates were inexplicably not included in the final models. No rationale was provided for the selection of the covariates, nor were their anticipated effects on treatment groups discussed. Further, this type of analysis is much like an observational study in which patients cannot be randomized to the specified covariates, thus raising issues that are conventionally associated with non-randomized studies.[76] In addition, there was no rationale for why the covariates were modelled using a fixed-effects approach. Finally, some models did not converge; therefore, not all of the covariates could be included, which leaves uncertain the extent to which adding these to the models would have improved our certainty that the results are valid. These methodological limitations significantly increase the uncertainty regarding the comparative benefits of FF/VI versus other ICS/LABA combinations.

A strength of the analysis is that model fit was assessed by evaluating the plot of the residuals. Additional strengths include reporting of the description of the type and values of the priors used for each network, the number of planned iterations, and the number of burn-ins until the models converged. However, while the authors commented on whether the models converged, they did not provide formal statistics to confirm goodness-of-fit; e.g., Bayesian information criteria or deviance information criteria.

A key feature of the IDC is the manufacturer's claim with respect to making inferences about the relative efficacy of disconnected networks; i.e., those that included treatments that were not linked via sequences of direct or IDCs. The manufacturer reported using the magnitude of τ for this purpose, claiming that if its value is 0, then "disconnected comparisons will be as reliable as direct comparisons." From the network diagrams, three of the four outcome networks feature disconnected comparisons. There were four, two, and three disconnected links in the PEF, exacerbations, and AQLQ networks, respectively. The manner in which data were synthesized across the disconnected links is unclear. It appears that the assumption was there was minimal, if any, variability in patient data between

treatments across trials. Despite the presence of disconnected comparisons, the authors classified τ as small for the PEF (τ = 6.426) and AQLQ (τ = 0.157) analyses, although they noted τ as moderate and very large for the FEV_1 (τ = 0.101) and exacerbations (τ = 0.431) analyses, respectively. Reliance on a single estimate of study-to-study variability such as τ is overly simplistic, and assuming minimal patient variability (or even no variability) between treatment groups across trials is unrealistic. This is particularly problematic when considering the fact that the authors assumed a normal distribution of the study-to-study variability when the coefficient of variation suggests otherwise. In particular, the posterior mean estimate of τ in the full covariate model for the AQLQ analysis is 0.157 with a standard deviation of 0.123. This corresponds to a coefficient of variation of about 80%, which suggests an exponential distribution rather than a normal distribution. Ultimately, this indicates there may be substantial heterogeneity (clinical or methodological) between studies, and that the treatment effect variations across studies were not at random. Altogether, the incorporation of disconnected treatments leaves uncertain the extent to which the network estimates are biased.

The manufacturer's approach to demonstrating non-inferiority of FF/VI versus other ICS/LABA combinations suffers from important limitations as well. First, it was not specified whether the original studies were designed as non-inferiority studies. To this end, it would be inappropriate to use data from trials in which investigators may not have guarded against unwarranted conclusions of non-inferiority, including not preserving the effects of the control treatment.[77] In addition, the authors do not specify the study populations from which they extracted and analyzed data; i.e., intention-to-treat (ITT) or per-protocol (PP). This is important to know, as ITT analyses are generally a less conservative approach versus PP analyses in non-inferiority designs. Further, the authors do not pre-specify the non-inferiority margins in the protocol, and their rationale for setting them was poorly described in the final report.

The validity of the manufacturer's IDC hinges on three important assumptions: homogeneity, transitivity, and consistency. To this end, it was not reported whether clinical, methodological, and statistical heterogeneity among the pairwise comparisons in the network were explored. Further, there was no exploration of intransitivity. As described above, although the IDC included four covariates in the hierarchical models, the rationale for their selection was not reported, and not all models converged, which leaves the utility of their inclusion — and whether intransitivity was minimized — uncertain. Lastly, despite having closed treatment loops in their networks, the authors did not formally evaluate the extent to which the direct evidence was consistent with the indirect evidence.

Conclusion

One manufacturer-provided IDC that compared the efficacy of FF/VI 100/25 mcg and FF/VI 200/25 mcg versus other medium- and high-dose ICS/LABA products for maintenance treatment of asthma among adolescents and adults — i.e., aged 12 years and older — was summarized and critically appraised. The IDC concluded that FF/VI 100/25 mcg and FF/VI 200/25 are "expected to be broadly comparable" to other ICS/LABA therapies across four efficacy outcomes, including mean change from baseline morning PEF, mean change from baseline FEV_1, mean change from baseline AQLQ total score, and annual rates of moderate or severe exacerbation.

However, there were several methodological and analytical limitations in the IDC. First, the baseline characteristics of patients enrolled in the included trials were inadequately reported, thereby precluding a full assessment of clinical heterogeneity across included trials and the external validity of the findings. In general, there was limited information regarding how key assumptions (such as heterogeneity and consistency) were evaluated and handled in the IDC. It was also unclear if the risks of bias in the included trials were assessed, thereby limiting the appraisal of the internal validity of the included studies, and ultimately the assessment of the underlying quality of the evidence. There was very little information provided with respect to approaches used to synthesize the evidence (including incorporating evidence from disconnected treatments) and to demonstrate non-inferiority of FF/VI 100/25 mcg and FF/VI 200/25 mcg versus other ICS/LABA combinations. The analysis only examined certain efficacy outcomes, and did not evaluate the relative harms or tolerability of FF/VI 100/25 mcg and FF/VI 200/25 mcg versus other ICS/LABA combinations. Hence, the comparative safety remains uncertain.

In conclusion, the numerous limitations with respect to the reporting and conduct of the manufacturer's IDC means there is a high degree of uncertainty regarding whether or not there are clinically relevant differences between FF/VI 100/25 mcg and FF/VI 200/25 mcg versus other ICS/LABA therapies for the maintenance treatment of asthma.

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18. PrSYMBICORT® TURBUHALER (budesonide/formoterol fumarate dihydrate):100 µg budesonide and 6 µg formoterol fumarate dihydrate 200 µg budesonide and 6 µg formoterol fumarate dihydrate 400 µg budesonide and 12 µg formoterol fumarate dihydrate Dry Powder Inhalers for Oral Inhalation Corticosteroid and bronchodilator for inhalation [product monograph] [Internet]. Mississauga (ON): AstraZeneca Canada Inc.; 2014 Apr 8. [cited 2015 Sep 21]. Available from: http://www.astrazeneca.ca/cs/BlobServer?blobcol=pdffile&blobheader=application%2Fpdf&blobheadername1=Content-Disposition&blobheadername2=MDT-Type&blobheadervalue1=inline%3B+filename%3DProduct-Monograph.pdf&blobheadervalue2=abinary%3B+charset%3DUTF-8&blobkey=id&blobnocache=true&blobtable=AZ_FixedURLPDF&blobwhere=1285585478642&ssbinary=true

19. PrZENHALE® (mometasone furoate / formoterol fumarate dihydrate inhalation aerosol): 50 mcg mometasone furoate / 5 mcg formoterol fumarate dihydrate 100 mcg mometasone furoate / 5 mcg formoterol fumarate dihydrate 200 mcg mometasone furoate / 5 mcg formoterol fumarate dihydrate Corticosteroid and long-acting beta2-agonist combination for oral inhalation [product monograph] [Internet]. Kirkland (QC): Merck Canada Inc.; 2014 Oct 21. [cited 2015 Sep 21]. Available from: http://www.merck.ca/assets/en/pdf/products/ZENHALE-PM_E.pdf

20. PrADVAIR® DISKUS®(salmeterol xinafoate/fluticasone propionate dry powder for inhalation) 50 mcg salmeterol (as the xinafoate salt) and 100 mcg fluticasone propionate; 50 mcg salmeterol (as the xinafoate salt) and 250 mcg fluticasone propionate; 50 mcg salmeterol (as the xinafoate salt) and 500 mcg fluticasone propionate; PrADVAIR® (salmeterol xinafoate/fluticasone propionate inhalation aerosol); 25 mcg salmeterol (as the xinafoate salt) and 125 mcg fluticasone propionate; 25 mcg salmeterol (as the xinafoate salt) and 250 mcg fluticasone propionate- Bronchodilator and Corticosteroid for Oral Inhalation [product monograph] [Internet]. Mississauga (ON): GlaxoSmithKline Inc.; 2015 Aug 5. [cited 2015 Sep 21]. Available from: http://www.gsk.ca/english/docs-pdf/product-monographs/Advair.pdf

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