Common Drug Review
Clinical Review Report

December 2015

Drug	Inhaled fluticasone furoate (Arnuity Ellipta) (100 mcg and 200 mcg)
Indication	Once-daily maintenance treatment of steroid-responsive bronchial asthma in patients aged 12 years and older
Listing request	As per indication
Dosage form(s)	Dry powder for oral inhalation, 100 mcg and 200 mcg
NOC date	September 21, 2015
Manufacturer	GlaxoSmithKline Inc.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

AE	adverse event
AQLQ	Standardized Asthma Quality of Life Questionnaire
AQLQ +12	Asthma Quality of Life Questionnaire developed for patients 12 years of age and older
CI	confidence interval
DB	double-blind
DPI	dry powder inhaler
FEV	forced expiratory volume
FEV_1	forced expiratory volume in one second
ICS	inhaled corticosteroid
ITT	intention-to-treat population
LABA	long-acting beta2-agonist
MCID	minimal clinically important difference
MPPI	minimal patient perceived improvement
PEF	peak expiratory flow
PP	per-protocol
RCT	randomized controlled trial
SABA	short-acting beta-agonist
SAE	serious adverse event
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Asthma is a common, chronic inflammatory disorder of the airways. Respiratory symptoms include cough, wheeze, dyspnea, and/or chest tightness. The prevalence of the disease in Canada has been estimated at 8.4% in adults and children aged 12 years and older.

Arnuity Ellipta (fluticasone furoate [FF] inhalation powder) is a once-daily inhaled corticosteroid (ICS) that is approved in Canada as maintenance treatment of steroid-responsive bronchial asthma in patients aged 12 years and older. Arnuity Ellipta is administered via a dry powder inhaler (DPI) called Ellipta, which is used also in three other products (Anoro Ellipta, Breo Ellipta, and Incruse Ellipta). FF is a corticosteroid with anti-inflammatory properties, and each FF DPI encompasses a foil strip with 30 blisters, each of which contains a white powder mixture of micronized FF (100 mcg or 200 mcg) and lactose. The recommended dose is 100 mcg to 200 mcg once daily.

The objective of this review was to perform a systematic review of the beneficial and harmful effects of FF 100 mcg and 200 mcg for the maintenance treatment of steroid-responsive bronchial asthma in patients aged 12 years and older.

Indication under review
Once-daily maintenance treatment of steroid-responsive bronchial asthma in patients aged 12 years and older.
Listing criteria requested by sponsor
For the prophylactic management of steroid-responsive bronchial asthma in patients aged 12 years and older.

Results and Interpretation

Included Studies

Five multi-centre, active-controlled, double-blind (DB), parallel-group, randomized controlled trials (RCTs) met the criteria for inclusion in the systematic review: FFA-687 (N = 601), HZA-827 (N = 610), HZA-829 (N = 587), FFA-059 (N = 343), and FFA-496 (N = 239). The included studies compared the efficacy of FF with that of fluticasone propionate (FP), combination fluticasone furoate/vilanterol (FF/VI), different FF doses, and/or placebo. One study (HZA-829) evaluated the non-inferiority of FF 200 mcg once daily compared with FP 500 twice daily. Study durations were eight weeks in Study FFA-687, 12 weeks in Study HZA-827, and 24 weeks in the three remaining studies. Trial participants were aged 37 to 47 years on average and had a history of asthma for more than 10 years. The majority were female. Baseline pre-bronchodilator forced expiratory volume in one second (FEV_1) ranged from 1.93 L to 2.28 L; the smallest volume was recorded in Study FFA-496 (1.93 L to 2.01 L) and Study HZA-829 (2.02 L to 2.07 L), and the largest volume was recorded in Study FFA-687 (2.16 L to 2.32 L). Per cent predicted FEV_1 ranged from 63.0% to 70.1%; the smallest percentages were recorded in Study FFA-496 (65.2% to 65.5%) and Study HZA-829 (63.0% to 63.6%). According to the clinical expert consulted on this review, this represents a typical patient population for asthma treatment in clinical practice. However, the clinical expert had some concerns about baseline severity in terms of percentage predicted FEV_1 and FEV_1 reversibility: the reported values might indicate sub-optimally treated asthma patients. Therefore, results might be biased in favour of the active treatment groups because patients in those groups would have had their treatment dose optimized, while placebo patients would have had their suboptimal active ICS switched to placebo. The patient populations

differed from one study to another in terms of pre-study asthma medication use; this might indicate different disease severity in the included studies. Specifically, Study HZA-829 recruited patients who had been treated with high-dose ICSs, which might indicate that these patients had more severe asthma than patients included in the other trials. Therefore, the results of non-inferiority testing in Study HZA-829 might not be generalizable to patients who have milder forms of asthma.

Efficacy

The incidence of severe asthma exacerbations was low (< 4% of patients) in all treatment groups except in Study FFA-496, in which approximately 13% of patients reported severe asthma exacerbation during the 24 weeks of treatment in both the FF 100 mcg and 200 mcg groups. The higher rate of exacerbations in this study relative to the other studies could not be explained. Differences in terms of asthma exacerbations between FF and placebo or FF and FP were not reported in the included studies.

The number of symptom-free days increased in all treatment groups, including the placebo group. However, FF 100 mcg and 200 mcg were shown to be associated with statistically significantly more symptom-free days than placebo in Studies FFA-687 and FFA-059 (the difference in symptom-free days between FF and placebo ranged from 8.8 days to 20.2 days). However, the difference observed between FF 100 mcg versus placebo was not statistically significant in Study HZA-827. Comparison of FF versus FP, in terms of symptom-free days, was not reported in the included studies. When FF was compared with the combination of FF/VI, it was shown that the combination therapy was associated with more symptom-free days; the differences (*P* values) were 12 days (0.001) and 8.4 days (0.01) in Studies HZA-827 and HZA-829, respectively.

The average increase from baseline to end point, in terms of FEV_1, in patients treated with FF 100 mcg or 200 mcg once daily ranged from 0.16 L to 0.37 L. Limited evidence indicates a minimal clinically important difference (MCID) for FEV_1 of 10.4% change from baseline; however, the included studies did not provide the corresponding percentage change from baseline. Therefore, the clinical significance of treatment could not be concluded. FF 100 mcg and 200 mcg were shown to be associated with statistically significantly larger changes from baseline to end point in FEV_1 than placebo (the mean difference in change from baseline between FF and placebo ranged from 0.136 L to 0.23 L). Compared with FP, FF 200 mcg once daily was associated with statistically non-inferior improvement in FEV_1 at a non-inferiority margin of –0.125 L (mean difference = 0.018 L; 95% confidence interval [CI], – 0.066 to 0.102). Statistical non-inferiority was consistent between the intention-to-treat (ITT) and per-protocol (PP) analyses. Based on these results, FF appears to improve FEV_1 relative to placebo. This effect was maintained though 24 weeks of treatment and appears to have had similar effects on FEV_1 improvement compared with FP. FF did not appear to be as effective as the combination FF/VI. The effects of FF 200 mcg on FEV were consistently greater than those produced by FF 100 mcg, although the difference between them did not reach statistical significance in any of the included studies.

FF compared with placebo showed a statistically significant difference in change from baseline in peak expiratory flow (PEF) in the eight-week and 12-week studies (FFA-687 and HZA-827); the differences ranged from 16 L/min to 22 L/min. However, the difference between FF 100 mcg and placebo was not statistically significant in Study FFA-059 at 24 weeks. The clinical significance of these differences is unknown. A comparison of FF versus FP, in terms of PEF, was not reported in the included studies. When FF was compared with the combination FF/VI, it was shown that the combination therapy was associated with better PEF results (larger change in PEF); the differences (*P* values) were 12 L/min (0.001) and 31 L/min (< 0.001), respectively. Based on PEF results, the effects of FF on PEF were similar to those seen for FEV, namely that FF had similar efficacy to FP, but was not as effective as combination FF/VI.

Relative to the effect of treatment on quality of life, Asthma Quality of Life Questionnaire developed for patients 12 years or older (AQLQ + 12) scores showed that in all treatment groups, including placebo-treated groups, the mean score increased by more than 0.5 points, which is the approximate MCID threshold proposed by the clinical expert. The comparative results of FF 100 mcg versus placebo was not consistent; it showed a statistically significant difference in Study FFA--0597 (mean difference = 0.33; *P* = 0.007), and a non-statistically significant difference in Study FFA-687 (mean difference = 0.15; *P* = 0.073). Formal comparisons between FF and FP in terms of AQLQ + 12 were not reported in the included studies.

All treatment groups in the included studies showed an increase in percentage of rescue-free 24-hour periods relative to baseline. FF 100 mcg and 200 mcg were associated with statistically significantly larger change from baseline to end point in the percentage of rescue-free days than placebo (the mean difference in change from baseline between FF and placebo ranged from 8.7 days to 18.9 days). A formal comparison of FF versus FP, in terms of percentage of rescue-free periods, was not reported in the included studies. When FF was compared with combination FF/VI, the combination therapy was associated with a higher percentage of rescue-free days (the differences [*P* values] were 10.6 days [< 0.001] and 11.7 days [< 0.001]), respectively.

There were no data available in the included studies for other outcomes of interest (e.g., dyspnea and nocturnal awakening).

Harms

The overall incidence of AEs in patients treated with FF was similar to those treated with FP, and both FF and FP were associated with a higher incidence of AEs than placebo. Serious adverse events (SAEs) were rare (< 3% across studies) and did not suggest any association with specific treatments.

The most common AEs reported in any treatment arm and across all studies were bronchitis, headache, nasopharyngitis, and upper respiratory tract infection. No deaths were reported in any of the included studies.

Conclusions

Five RCTs were included in which FF 100 mcg and 200 mcg were studied for eight weeks to 24 weeks in patients aged 12 years and older with steroid-responsive bronchial asthma. Other groups in these RCTs were treated with FP (100 mcg, 250 mcg, or 500 mcg twice daily), combination FF/VI (100 mcg/25 mcg or 200 mcg/25 mcg daily), or placebo. The results suggest that, compared with placebo, FP 100 mcg and 200 mcg both improved respiratory measures (FEV and PEF), reduced the incidence of asthma exacerbations, and increased the number of days without asthma symptoms though 24 weeks. However, FF does not appear to consistently improve quality of life.

No statistically significant differences between the FF 100 mcg and 200 mcg doses were reported in the included studies. Only limited conclusions regarding the comparative efficacy between FF and FP can be made, as no formal statistical analyses comparing FF and FP were made in the included studies other than in one non-inferiority trial. Trials were inadequately powered to assess outcomes identified as important by patients and were of insufficient duration to assess long-term outcomes with a medication routinely used in chronic asthma. However, FF appears to have similar efficacy compared with equivalent doses of FP. FF is less effective than combination FF/VI. Whether this conclusion applies for exposure periods that exceed 24 weeks is unknown. FF and FP appear to have similar harms profiles, although longer-term studies are needed to elucidate the harms of FF beyond 24 weeks of exposure.

TABLE 1: SUMMARY OF RESULTS

	FFA-687 (8 wks)				HZA-827 (12 wks)			HZA-829 (24 wks)			FFA-059 (24 wks)			FFA-496 (24 wks)	
Drug/Dosage (mcg)	**FF 100**	**FF 200**	**FP 100**	**PBO**	**FF 100**	**FF/VI 100/25**	**PBO**	**FF 200**	**FF/VI 200/25**	**FP 500**	**FF 100**	**FP 250**	**PBO**	**FF 100**	**FF 200**
Total, N	**110**	**95**	**102**	**94**	**205**	**201**	**203**	**194**	**197**	**195**	**114**	**114**	**115**	**108**	**111**
Severe asthma exacerbations															
n (%)	3 (3)	1 (1)	2 (2)	0	4 (2)	1 (< 1)	9 (4)	6 (3)	0	2 (1)	2 (2)	2 (2)	4 (3)	14 (13)	13 (12)
% of symptom-free 24-hour periods															
LS mean change,[a] (SE)	38.7 (3.0)	31.7 (3.2)	33.3 (3.1)	18.4 (3.2)	20.4 (2.1)	32.5 (2.1)	14.6 (2.2)	21.0 (2.32)	29.3 (2.29)	24.5 (2.31)	19.3 (2.8)	19.2 (2.8)	10.4 (2.8)	17.5 (2.80)	19.6 (2.79)
Difference vs. PBO	**20.2[b]**	**13.2[b]**	**14.9[b]**	NA	5.8	**18.0[b]**	NA	NA	NA	NA	**8.9[b]**	**8.8[b]**	NA	NA	
FF vs. active arms	NR	NA			NA	**–12.1[b]**	NA	NA	**–8.4[b]**	NR	NR	NA		–2.1	
FEV_1 (absolute volume), L															
LS mean change,[a] (SE)	0.34 (0.04)	0.37 (0.04)	0.24 (0.04)	0.14 (0.04)	0.33 (0.03)	0.37 (0.03)	0.20 (0.03)	0.20 (0.03)	0.39 (0.03)	0.18 (0.03)	0.16 (0.04)	0.16 (0.04)	0.02 (0.04)	0.21 (0.04)	0.28 (0.04)
Difference vs. PBO	**0.20[b]**	**0.23[a]**	0.11	NA	**0.136[b]**	**0.172[b]**	NA	NA	NA	NA	**0.15[b]**	**0.15[b]**	NA		
FF vs. active arms	NR	NR	NA	NA	–0.04	NA	NA	NA	**–0.19[a]**	–0.018	NR	NA	NA	0.077[a]	
PEF (L/min)															
LS mean change,[a] (SE)	25.7 (3.90)	31.3 (4.20)	24.4 (4.04)	9.6 (4.21)	14.1 (2.34)	26.4 (2.35)	–1.8 (2.36)	9.1 (2.98)	39.8 (2.93)	13.6 (2.96)	1.5 (3.39)	4.3 (3.4)	–1.3 (3.36)	5.9 (3.26)	7.2 (3.25)
Difference vs. PBO	**16.1[b]**	**21.7[b]**	**14.9[b]**	NA	**15.9[b]**	**28.2[b]**	NA	NA			2.8	5.5	NA	NA	
FF vs. active arms	NR		NA		**NA**	**–12.3[b]**	NA	NA	**-30.7[b]**	NR	NR	NA		–1.3 (–10.4, 7.8)	
AQLQ + 12 Total Score															
LS mean change,[a] (SE)					0.76 (0.06)	0.91 (0.06)	0.61 (0.06)	0.88 (0.07)	0.93 (0.07)	0.90 (0.07)	0.84 (0.08)	0.68 (0.08)	0.51 (0.09)		
Difference vs. PBO					0.15	**0.30[a]**	NA	NA			**0.33[a]**	0.16	NA		
FF vs. active arms					–0.15	NA		NA	0.05	NR	NR	NA			
AEs, N (%)	35 (32)	27 (28)	35 (34)	24 (26)	52 (25)	59 (29)	43 (21)	90 (46)	92 (47)	97 (50)	60 (53)	48 (42)	46 (40)	70 (59)	75 (63)

	FFA-687 (8 wks)				HZA-827 (12 wks)			HZA-829 (24 wks)			FFA-059 (24 wks)			FFA-496 (24 wks)	
Drug/Dosage (mcg)	**FF 100**	**FF 200**	**FP 100**	**PBO**	**FF 100**	**FF/VI 100/25**	**PBO**	**FF 200**	**FF/VI 200/25**	**FP 500**	**FF 100**	**FP 250**	**PBO**	**FF 100**	**FF 200**
Total, N	**110**	**95**	**102**	**94**	**205**	**201**	**203**	**194**	**197**	**195**	**114**	**114**	**115**	**108**	**111**
SAEs,[c] N (%)	1 (1)	0	2 (2)	0	1 (< 1)	0	0	1 (< 1)	6 (3)	2 (1)	4	1	2	3 (3)	4 (3)
WDAEs, N (%)	2 (2)	1 (1)	2 (2)	0	0	2 (< 1)	1 (< 1)	3 (2)	7 (4)	2 (1)	3 (3)	3 (3)	2 (2)	2 (2)	2 (2)
Infections and infestations	15 (14)	11 (12)	9 (9)	6 (6)	31 (15)	34 (17)	22 (11)	61 (31)	59 (30)	70 (36)	47 (41)	21 (18)	31 (27)	49 (41)	48 (40)

AE = adverse event; ANCOVA = analysis of covariance; AQLQ = Asthma Quality of Life Questionnaire; FEV_1 = forced expiratory volume in one second measured at evening trough; FF = fluticasone furoate; FP = fluticasone propionate; NA = not applicable; NR = not reported; PEF = peak expiratory flow measured in the evening; PBO = placebo; SAE = serious adverse event; SD = standard deviation; VI = vilanterol; vs = versus; WDAE = withdrawal due to adverse event; wks = weeks.

[a] Least squares means adjusted in the ANCOVA model.

[b]. Statistically significant results.

[c] On-treatment SAEs.

Source: Clinical Study Reports.[1-6]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Asthma is a common, chronic inflammatory disease of the airways. The term "current asthma" defines a chronic disease process that has been active over the past 12 months, as determined through a thorough asthma and allergy clinical history consistent with this syndrome. This includes respiratory symptoms of cough, wheeze, dyspnea and/or chest tightness with associated confirmatory physiologic testing (spirometry with evaluation of post-bronchodilator reversibility; day-to-day variability in spirometry; evidence of airway hyper-responsiveness as determined most commonly by a methacholine or exercise challenge).[7,8] In Canada, asthma is evaluated and managed by a variety of medical specialists as well as other independent practitioners (nurse practitioners, pharmacists, respiratory therapists), particularly in geographically diverse locations and in large rural/remote regions such as the territories, the Prairie provinces, and the Atlantic provinces.

Based on administrative databases, asthma prevalence has been estimated at 8.4% of adolescents and adults (aged 12 years and older), and 13% of children (younger than 12 years).[9,10] An administrative database evaluation within Ontario estimates a 1-in-3 lifetime prevalence of asthma in that province.[11,12]

Asthma can be overdiagnosed just as much as being underdiagnosed.[13-16] Overdiagnosis of asthma can cost the Canadian health care system, and may delay the appropriate diagnosis of the condition in an individual with serious other disorders mislabelled as asthma (e.g., disorders of the pulmonary parenchyma, disorders of the pulmonary vascular system, cardiac disease, deconditioning, and certain DSM-IV disorders such as anxiety and depression, which commonly present in a similar fashion). As such, evaluation of a drug's efficacy within "real-world" clinical trials — as opposed to trials specifically performed for regulatory approvals — needs to be taken into consideration, while noting that inhaled medications have a strong placebo effect. This placebo effect should be considered in cost analyses, particularly in comparisons of combination inhalers (long-acting beta2-agonist [LABA]) and inhaled corticosteroids (ICSs) as opposed to ICSs alone.

1.2 Standards of Therapy

ICSs remain the first-line therapy for long-term control of mild, moderate, and severe persistent asthma for all age groups, according to national and international guidelines. [7,8] The therapeutic effect of corticosteroids is due to their anti-inflammatory properties, resulting in improved pulmonary function, asthma symptom control, and decreased airway hyper-responsiveness. The second-line agents that are most often used for asthma treatment are LABAs or leukotriene modifiers. Systemic steroids are often used for patients with severe asthma. In Canada, the available ICS therapies for asthma are fluticasone propionate (FP), mometasone furoate, budesonide, beclomethasone dipropionate, and ciclesonide (Table 2). In addition, there are various combinations of ICS/LABA inhalers available for the control of asthma.

1.3 Drug

Fluticasone furoate (FF) is a corticosteroid with anti-inflammatory properties, administered by oral inhalation via a novel dry powder inhaler (NDPI). FF dry powder inhaler (DPI) encompasses a foil strip with 30 blisters. Each blister contains a white powder mixture of micronized FF (100 mcg or 200 mcg) and lactose. At the recommended once-daily dose of 100 mcg to 200 mcg per day, FF is indicated for the maintenance treatment of steroid-responsive bronchial asthma in patients aged 12 years and older.

Indication under review
Once-daily maintenance treatment of steroid-responsive bronchial asthma in patients aged 12 years and older.
Listing criteria requested by sponsor
For the prophylactic management of steroid-responsive bronchial asthma in patients aged 12 years and older.

TABLE 2: KEY CHARACTERISTICS OF INHALED CORTICOSTEROID MONOTHERAPIES FOR BRONCHIAL ASTHMA

	Fluticasone Furoate (ARNUITY ELLIPTA[17])	Fluticasone Propionate (FLOVENT DISKUS/HFA[18])	Mometasone Furoate (ASMANEX[19])	Budesonide (PULMICORT[20])	Beclomethasone (QVAR[21])	Ciclesonide (ALVESCO)
Mechanism of Action	Synthetic trifluorinated corticosteroid. The precise mechanism through which FF affects asthma symptoms is not known.	Glucocorticoid anti-inflammatory steroid.	A corticosteroid demonstrating anti-inflammatory properties. The precise mechanism of corticosteroid action on asthma is not known.	Synthetic glucocorticosteroid with strong topical and weak systemic effects.	A synthetic corticosteroid chemically related to dexamethasone, it probably acts as a topical anti-inflammatory agent at the site of deposition in the bronchial tree.	It has an active glucocorticoid metabolite, 21 desmethylpropionyl-ciclesonide (M1), that binds to glucocorticoid receptors in the lung, resulting in local anti-inflammatory activity.
Health Canada-Approved Indication	Maintenance treatment of steroid-responsive bronchial asthma in patients aged 12 years and older.	Prophylactic management of steroid-responsive bronchial asthma in adults and children (aged 12 months and older).	Prophylactic management of steroid-responsive bronchial asthma in patients aged 4 years and older.	For patients (aged 6 years and older) with bronchial asthma who require inhaled steroids and in patients for whom a reduction of systemic glucocorticoids is desirable.	Prophylactic management of steroid-responsive bronchial asthma in patients aged 5 years and older.	Prophylactic management of steroid-responsive bronchial asthma in adults, adolescents, and children aged 6 years and older.
Route of Administration	Oral inhalation					

	Fluticasone Furoate (ARNUITY ELLIPTA[17])	Fluticasone Propionate (FLOVENT DISKUS/HFA[18])	Mometasone Furoate (ASMANEX[19])	Budesonide (PULMICORT[20])	Beclomethasone (QVAR[21])	Ciclesonide (ALVESCO)
Recommended Dose	100 mcg to 200 mcg q.d.	Dose depends on asthma severity and patient's response: Mild: 100 mcg to 250 mcg b.i.d. Moderate: 250 mcg to 500 mcg b.i.d. Severe: 500 mcg b.i.d.	< 12 years: 100 mcg q.d. ≥ 12 years: 200 mcg q.d., 200 mcg b.i.d., or 400 mcg q.d.	Starting dose: 6 to 12 years: 100 mcg to-200 mcg b.i.d. ≥ 12 years: 400 mcg to 2,400 mcg divided into 2 to 4 administrations.[a] The maintenance dose is 200 mcg to 400 mcg b.i.d.	5 to 11 years: 50 mcg to 100 mcg b.i.d. ≥ 12 years: dose depends on asthma severity Mild: 50 mcg to 100 mcg b.i.d. Moderate: 100 mcg to 250 mcg b.i.d. Severe: 300 mcg to 400 mcg b.i.d.	6 to 11 years: 100 mcg to 200 mcg q.d. ≥ 12 years: 400 mcg q.d. (dose range is 100 mcg to 800 mcg)
	The lowest dose required to maintain good asthma control should be used.					
Serious Side Effects/ Safety Issues (as Reported in Product Monographs)	Thrush (common), bronchitis (common), pneumonia, asthma exacerbations, decreased adrenal function, glaucoma, cataract, allergic reaction, and bone fractures or osteoporosis.	Thrush (very common), allergic reactions (common), Churg–Strauss syndrome, esophageal candidiasis, slowed growth in children and adolescents, and Cushing syndrome.	Thrush (common), serious allergic reactions, worsening asthma or sudden asthma attack, increased heart rate, respiratory distress, decreased platelets, Churg–Strauss syndrome, glaucoma, cataract, and decreased adrenal function.	Bronchospasm and severe allergic reactions.	No SAEs were signalled in the PM.	Sudden wheezing and chest pain or tightness.
	In general, ICS therapy may be associated with dose-dependent increases in the incidence of ocular complications, reduced bone density, suppression of the HPA axis responsiveness to stress, and inhibition of growth velocity in children.					

		Fluticasone Furoate (ARNUITY ELLIPTA[17])	Fluticasone Propionate (FLOVENT DISKUS/HFA[18])	Mometasone Furoate (ASMANEX[19])	Budesonide (PULMICORT[20])	Beclomethasone (QVAR[21])	Ciclesonide (ALVESCO)
Dose Convergence	**High**	200 mcg	> 500 mcg to 100 mcg	≥ 800 mcg	> 800 mcg to 1,600 mcg	> 1,000 mcg to 2,000 mcg	> 320 mcg to 1,280 mcg
	Medium	100 mcg	> 250 mcg to 500 mcg	≥ 400 mcg	> 400 mcg to 800 mcg	> 500 mcg to 1,000 mcg	> 160 mcg to 320 mcg
	Low		100 mcg to 250 mcg	200 mcg	200 mcg to 400 mcg	200 mcg to 500 mcg	80 mcg to 160 mcg

b.i.d. = twice daily; HPA = hypothalamic–pituitary–adrenal; ICS = inhaled corticosteroid; PM = product monograph; q.d. = once daily.
[a] During severe asthma and while reducing or discontinuing oral glucocorticoids.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of FF 100 mcg and 200 mcg for the maintenance treatment of steroid-responsive bronchial asthma in patients aged 12 years and older.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase 3 studies were selected for inclusion based on the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Patients with steroid-responsive bronchial asthma aged ≥ 12 years Subgroups of interest: • Severity of Asthma
Intervention	FF 100 mcg or 200 mcg once daily
Comparators	• Corticosteroids (inhaled and oral) • ICS/LABA • Leukotriene antagonists (i.e., zafirlukast and montelukast) ± ICS +/- LABA • Anti-IgE monoclonal antibodies (i.e., omalizumab) ± ICS ± LABA (All ± SABAs)
Outcomes	**Key efficacy outcomes:** • Incidence of acute exacerbations of asthma • Number of asthma symptom-free days • Incidence of dyspnea • Incidence of nocturnal awakening • Change in pulmonary function (e.g., FVC, FEV_1, PEF) • Quality of life • Per cent of rescue-free 24-hour periods **Other efficacy outcomes:** • Incidence of missed work/school days • Incidence of hospitalizations, ER visits, or MD visits • Ease of use of, and adherence to, treatment **Harms outcomes:** • AEs, SAEs, WDAEs, mortality **Notable Harms:** • Growth rates (ages 12 to 17 years), infections (systemic and local), adrenal suppression, contusion, renal system AEs
Study Design	Published and unpublished phase 3 RCTs

AE = adverse event; DB = double-blind; ER = emergency room; FEV_1 = forced expiratory volume in 1 second; FF = fluticasone furoate; FVC = forced vital capacity; ICS = inhaled corticosteroid; IgE = immunoglobulin E; LABA = long-acting beta2-agonist; PEF = peak expiratory flow; RCT = randomized controlled trial; SABA = short-acting beta2-agonist; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–July 26, 2015) with in-process records and daily updates via Ovid; Embase (1974–July 26, 2015) 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 Arnuity Ellipta and Fluticasone Furoate.

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 July 26, 2015. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee on November 18, 2015. Regular search updates were performed on databases that do not provide alert services.

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

Two CADTH Common Drug Review clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in APPENDIX 3.

3. RESULTS

3.1 Findings From the Literature

A total of 257 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and described in Section 3.1. A list of excluded studies is presented in APPENDIX 3.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

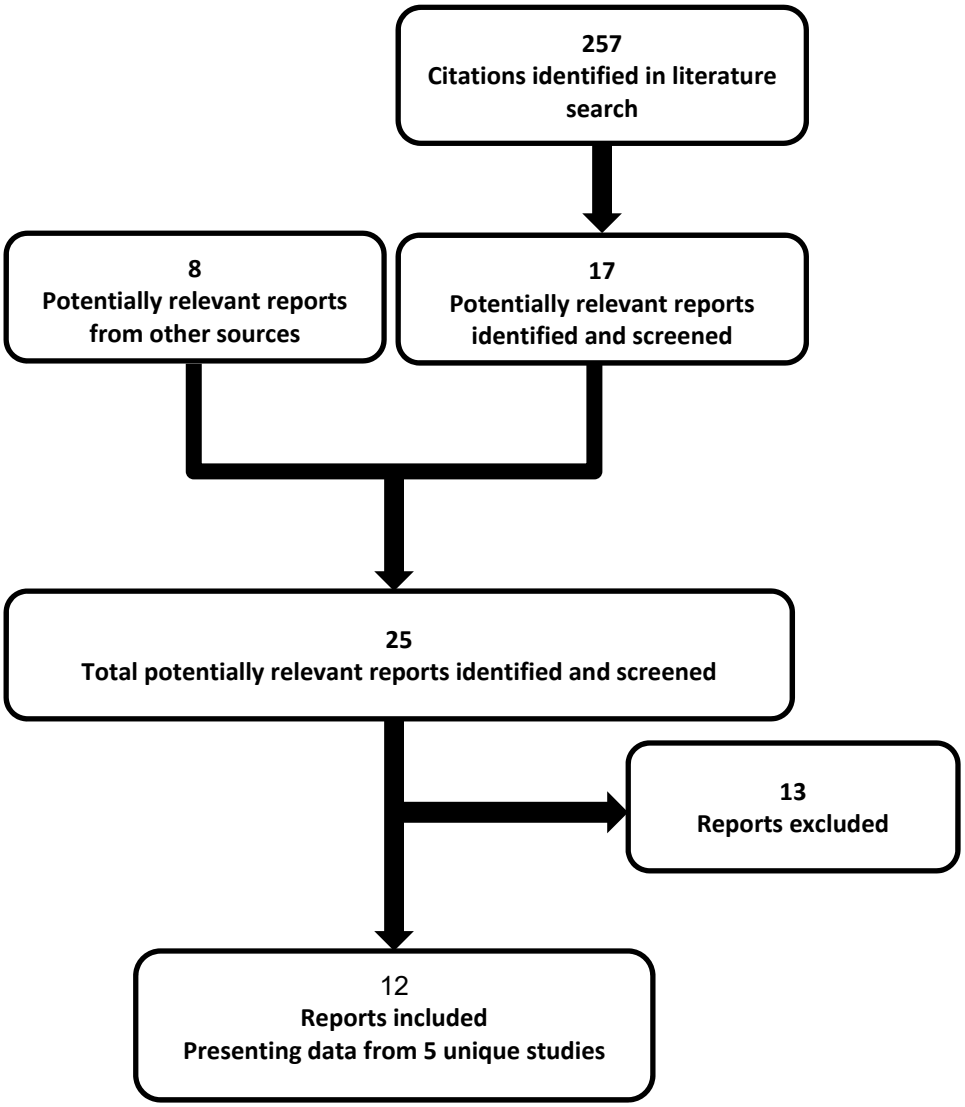

TABLE 4: DETAILS OF INCLUDED STUDIES

		FFA-687	HZA-827	HZA-829	FFA-059	FFA-496
DESIGNS & POPULATIONS	**Study Design**	DB, double-dummy RCT, with active reference group(s)				DB RCT
	Locations	North America, Europe, Central America, South America, and Asia-Pacific	Germany, Japan, Poland, Romania, Ukraine, and US	Russia, US, Romania, Germany, Poland, and Japan	US, Germany, Romania, Poland, and Belgium	US, Argentina, Russia, Chile, Mexico, and France
	Study Period	Dec. 2007 → Oct. 2008	Aug. 2010 → Oct. 2011	June 2010 → Oct. 2011	June 2010 → Jan. 2012	Sept. 2011 → Oct. 2012
	Randomized (N)	601	610	587	343	239
	Inclusion Criteria	• ≥ 12 years of age; ≥ 12 weeks diagnosis of asthma; ≥ 4 weeks of using a stable dose of ICS • 40% to 90% FEV_1 (pre-bronchodilator) (at screening visit and end-of-run-in period) • ≥ 12% and ≥ 200 mL evening reversibility of FEV_1 within 10 to 40 minutes following 2 to 4 inhalations of albuterol/salbutamol inhalation aerosol • Albuterol/salbutamol use on at least 4 of the last 7 consecutive days of the run-in period.				
	Exclusion Criteria	• History of life-threatening asthma within the last 10 years, or any respiratory infection that had not resolved within 4 weeks of visit 1 and led to a change in asthma management • Any asthma exacerbation requiring treatment with oral corticosteroids or that resulted in overnight hospitalization requiring additional treatment for asthma within 6 months prior to screening • Visual evidence of oropharyngeal candidiasis at screening visit.				
DRUGS	**Intervention**	FF via NDPI (once daily in the evening)				
		25 mcg, 50 mcg, 100 mcg, or 200 mcg	100 mcg	200 mcg	100 mcg	100 mcg
	Comparator(s)	• FP 100 mcg via DISKUS/ACCUHALER (b.i.d.) • Placebo	• FF 100 mcg + VI 25 mcg (q.d.) • Placebo	• FF 200 mcg + VI 25 mcg (q.d.) • FP 500 mcg (b.i.d.)	• FP 250 mcg via DISKUS/ ACCUHALER (b.i.d.) • Placebo	• FF 200 mcg (q.d.)
DURATION	**Phase**	Phase 2	Phase 3			
	Run-in	4 weeks				
	DB	8 weeks	12 weeks	24 weeks		
	Follow-up	1 week				
OUTCOMES	**Primary End Point**	Trough evening (pre-bronchodilator and pre-dose) FEV_1				
	Co-primary End Point	NA	Weighted mean FEV_1 (0 to 24 hours post-dose) FEV_1[a]		NA	
	Other End Points	• Percentage of rescue-free 24-hour periods • Percentage of symptom-free 24-hour periods • Trough (pre-dose and pre-rescue bronchodilator) evening and morning PEF				

		FFA-687	HZA-827	HZA-829	FFA-059	FFA-496
	Publications	Bateman et al. 2012[22]	O'Byrne et al. 2014[23]	Bleeker et al. 2014[24]	Lotvall et al. 2014[25]	Woodcock et al. 2014[26]

b.i.d. = twice daily; CSR = Clinical Study Report; DB = double-blind; FEV_1 = forced expiratory volume in 1 second; FF = fluticasone furoate; FP = fluticasone propionate; ICS = inhaled corticosteroid; NA = not applicable; NDPI = novel dry powder inhaler; PEF = peak expiratory flow; q.d. = once daily; RCT = randomized controlled trial; SABA = short-acting beta2-agonist; VI = vilanterol.

[a] Weighted mean was calculated over a 24-hour post-dose period on a small percentage of the included patients.

Note: Two additional reports were included.[27,28]

Source: Clinical Study Reports.[1-4,6]

3.2 Included Studies

3.2.1 Description of Studies

Five manufacturer-sponsored, multi-centre, active-controlled, parallel-group, randomized controlled trials (RCTs) met the criteria for inclusion in the systematic review. The included studies were double-blind (DB). Four trials were double-dummy, as they included placebo groups in addition to the active comparators in three studies, and one study (HZA-829) had two active comparator groups. None of the included studies had the primary objective of comparing FF with other ICSs. Rather, the comparison of FF with other ICSs was secondary to the primary comparison of one dosage of FF with another, with placebo, or with the combination therapy of FF plus vilanterol (FF/VI). One study, HZA-829, had a secondary objective to test the non-inferiority of FF 200 mcg once daily versus FP 500 mcg twice daily. The included studies differed in their treatment duration, from eight weeks (Study FFA-687) to 24 weeks (Studies HZA-829, FFA-059, and FFA-496).

3.2.2 Populations

a) Inclusion and Exclusion Criteria

Screening eligibility criteria were similar in the included studies, except that there were a few differences relative to the patients' pre-study asthma medication. In Study FFA-687, for example, patients must have been using a non-corticosteroid controller or short-acting beta2-agonist (SABA) bronchodilator alone (with no ICS use for at least six weeks) for at least three months preceding screening. In the remaining four studies, patients must have been using a stable ICS dose for at least one month before screening. Pre-screening ICS dose varied from low to medium in Study HZA-827, was medium in Study HZA-829, and varied from medium to high in Study FFA-496; the pre-screening ICS dose range was not reported for Study FFA-059. Likewise, the included studies differed with regard to the eligibility of patients who had been using LABA in combination with ICS. Studies HZA-827 and HZA-829 allowed patients who used LABAs during the period preceding the study to enter the run-in period, but these studies reported that those patients were not allowed to continue their LABA medication during the study period. The remaining three studies included patients who used ICS monotherapy without LABA. In all studies, patients must have been able to replace their current SABA with albuterol/salbutamol inhalation aerosol for use as needed for the duration of the study. Current smokers, patients with a smoking history of 10 pack-years or more, and patients who had used tobacco products within one year prior to the study were not eligible for inclusion.

Patients meeting all the screening eligibility criteria entered a four-week run-in period during which they remained on their baseline ICS medication, except in Study FFA-687. In addition, all patients were provided with albuterol/salbutamol for relief of asthma symptoms. During the run-in and DB treatment periods, patients maintained an electronic daily diary to record morning and evening peak expiratory flow (PEF), asthma symptom score, and rescue albuterol/salbutamol use. Patients were contacted by telephone during run-in to ensure compliance with run-in medication and diary monitoring.

Randomization eligibility criteria were similar in the included studies except for one element: asthma symptom score. Asthma symptom score is derived from a patient-reported questionnaire about the occurrence of asthma symptoms; it includes two main sections: daytime (five items) and nighttime (four items). Items are graded in ordinal order from 0 to 5 and from 0 to 4, respectively, and the total score can range from 0 to 9; higher scores indicate more severe symptoms. In three studies (FFA-687, HZA-827, and FFA-059), patients should have had an asthma symptom score of ≥ 1 at the end of run-in period, while Study HZA-829 reported a threshold score of 3. Study FFA-496 did not report on asthma symptom score.

b) Baseline Characteristics

The majority of patients in the included studies were white (67% to 86%), mostly female (50% to 68%), and their mean age ranged from 37 years to 47 years (Table 5). Four studies included patients younger than 18 years old, and the percentage of this subgroup of patients ranged from 1% to 16%. 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 FFA-496 reported the longest duration (20 years to 22 years) (Table 6). Past asthma treatment with LABA varied among the included studies; three studies (HZA-827, HZA-829 and FFA-493) reported that asthma was managed with LABAs in 24% to 41% of the included patients. Study FFA-059 reported that 4% to 7% of the included patients had previous exposure to LABAs for the treatment of asthma. Only three participants in Study FFA-687 reported past use of LABAs.

Asthma severity at baseline was measured by forced expiratory volume in one second (FEV_1). Screening values of pre-bronchodilator volume ranged from 1.93 L to 2.28 L; the smallest volume was recorded for Study FFA-496 (1.93 L to 2.01 L) and Study HZA-829 (2.02 L to 2.07 L), and the largest volume was recorded in Study FFA-687 (2.16 L to 2.32 L) (Table 7). Per cent predicted FEV_1 ranged from 63.0% to 70.1%; the smallest percentages were recorded in Study FFA-496 (65.2% to 65.5%) and Study HZA-829 (63.0% to 63.6%).

TABLE 5: SUMMARY OF PATIENTS' DEMOGRAPHICS

	FFA-687 (8 weeks)				HZA-827 (12 weeks)			HZA-829 (24 weeks)			FFA-059 (24 weeks)			FFA-496 (24 weeks)	
Drug/Dosage (mcg)	**FF 100**	**FF 200**	**FP 100**	**PBO**	**FF 100**	**FF/VI 100/25**	**PBO**	**FF 200**	**FF/VI 200/25**	**FP 500**	**FF 100**	**FP 250**	**PBO**	**FF 100**	**FF 200**
ITT (N)	**110**	**95**	**102**	**94**	**205**	**201**	**203**	**194**	**197**	**195**	**114**	**114**	**115**	**108**	**111**
Male, n (%)	50 (45)	35 (37)	46 (45)	47 (50)	79 (39)	85 (42)	92 (45)	81 (42)	81 (41)	79 (41)	51 (45)	42 (37)	47 (41)	38 (32)	40 (34)
Age in years, mean (SD)	37 (15)	41 (16)	40 (15)	39 (16)	40 (16)	41 (16)	38 (17)	45 (14)	47 (15)	47 (14)	40 (16)	41 (16)	40 (18)	47 (15)	45 (16)
< 18, n (%)	NR	NR	NR	NR	28 (1)	21 (10)	33 (16)	7 (4)	8 (4)	8 (4)	17 (15)	11 (10)	18 (16)	7 (6)	6 (5)
18 to 65, n (%)	NR	NR	NR	NR	161 (76)	169 (84)	160 (79)	173 (89)	167 (85)	171 (88)	93 (82)	98 (86)	92 (80)	89 (82)	96 (86)
≥ 65, n (%)	NR	NR	NR	NR	16 (8)	11 (5)	10 (5)	14 (7)	22 (11)	16 (8)	4 (4)	5 (4)	5 (4)	12 (11)	9 (8)
White, n (%)	76 (69)	64 (67)	74 (73)	69 (73)	171 (83)	172 (86)	169 (83)	165 (85)	165 (84)	162 (83)	90 (80)	92 (81)	88 (77)	94 (87)	96 (86)
Black, n (%)	8 (7)	6 (6)	5 (5)	5 (5)	16 (8)	13 (6)	14 (7)	16 (8)	16 (8)	19 (10)	22 (19)	19 (17)	23 (20)	2 (2)	1 (< 1%)

FF = fluticasone furoate (100 mcg or 200 mcg once daily); FP = fluticasone propionate (100 mcg, 250 mcg, or 500 mcg twice daily); ITT = intention-to-treat; NR = not reported; PBO = placebo; SD = standard deviation; VI = vilanterol.
Source: Clinical Study Reports.[1-4,6]

TABLE 6: SUMMARY OF ASTHMA AND MEDICAL HISTORY

	FFA-687 (8 weeks)				HZA-827 (12 weeks)			HZA-829 (24 weeks)			FFA-059 (24 weeks)			FFA-496 (24 weeks)	
Drug/Dosage (mcg)	**FF 100**	**FF 200**	**FP 100**	**PBO**	**FF 100**	**FF/VI 100/25**	**PBO**	**FF 200**	**FF/VI 200/25**	**FP 500**	**FF 100**	**FP 250**	**PBO**	**FF 100**	**FF 200**
ITT (N)	**100**	**95**	**102**	**94**	**205**	**201**	**203**	**194**	**197**	**195**	**114**	**114**	**115**	**108**	**111**
Duration of asthma, years															
Mean (SD)	NR	NR	NR	NR	13 (12)	12 (12)	11 (10)	15 (12)	17 (13)	15 (13)	18 (13)	19 (15)	18 (14)	20 (16)	22 (15)
< 1 year, n (%)	4 (< 4)	6 (6)	2 (< 2)	2 (2)	10 (5)	17 (8)	16 (7)	6 (3)	2 (2)	3 (2)	1 (< 1)	0	1 (< 1)	1 (< 1)	3 (3)
1 to 5 years, n (%)	22 (20)	16 (17)	17 (17)	14 (15)	44 (21)	54 (27)	52 (26)	27 (14)	31 (16)	35 (18)	11 (10)	19 (17)	16 (14)	17 (14)	12 (10)
5 to 10 years, n (%)	19 (17)	22 (23)	16 (16)	13 (14)	44 (21)	47 (23)	36 (18)	49 (25)	35 (18)	45 (23)	24 (21)	20 (18)	21 (18)	20 (17)	12 (10)
≥ 10 years, n (%)	65 (59)	51 (54)	67 (66)	65 (69)	107 (52)	83 (41)	99 (49)	112 (58)	129 (65)	112 (57)	78 (68)	75 (66)	77 (67)	80 (68)	92 (77)
Use of asthma medication, n (%)															
Any medication	110 (100)	95 (100)	102 (100)	94 (100)	205 (100)	200 (> 99)	202 (> 99)	194 (100)	197 (100)	195 (100)	112 (98)	114 (100)	114 (> 99)	108 (100)	111 (100)
FP	1 (< 1)	3 (3)	2 (2)	0	108 (53)	97 (48)	96 (47)	113 (58)	126 (64)	115 (59)	48 (42)	55 (48)	55 (48)	70 (65)	72 (65)
Salbutamol	102 (93)	90 (95)	98 (96)	85 (90)	135 (66)	134 (67)	146 (72)	69 (36)	77 (39)	68 (35)	41 (36)	39 (34)	44 (38)	11 (9)	7 (6)
Budesonide	0	1 (1)	0	1 (1)	42 (20)	50 (25)	47 (23)	33 (17)	37 (19)	42 (22)	30 (26)	33 (29)	32 (28)	19 (18)	23 (21)
Beclomethasone dipropionate	NR	NR	NR	NR	29 (14)	29 (14)	22 (11)	30 (15)	21 (11)	19 (10)	17 (15)	20 (18)	14 (12)	8 (7)	10 (9)
Salmeterol xinafoate + FP	1 (1)	0	2 (2)	0	54 (26)	48 (24)	55 (27)	79 (41)	70 (36)	74 (38)	8 (7)	8 (7)	5 (4)	40 (37)	30 (27)
Peripheral eosinophil at screening visit,[a] n (%)															
High	18 (17)	23 (25)	13 (13)	14 (15)	14 (7)	20 (10)	14 (7)	16 (9)	16 (9)	16 (9)	6 (5)	10 (9)	10 (9)	15 (14)	18 (17)
Normal	NR	NR	NR	NR	170 (86)	157 (82)	165 (83)	146 (84)	149 (84)	152 (87)	103 (91)	92 (82)	95 (84)	84 (80)	79 (75)
Low	NR	NR	NR	NR	13 (7)	14 (7)	19 (10)	11 (6)	13 (7)	7 (4)	4 (4)	10	8 (7)	6 (6)	9 (8)

	FFA-687 (8 weeks)				HZA-827 (12 weeks)			HZA-829 (24 weeks)			FFA-059 (24 weeks)			FFA-496 (24 weeks)	
Drug/Dosage (mcg)	**FF 100**	**FF 200**	**FP 100**	**PBO**	**FF 100**	**FF/VI 100/25**	**PBO**	**FF 200**	**FF/VI 200/25**	**FP 500**	**FF 100**	**FP 250**	**PBO**	**FF 100**	**FF 200**
ITT (N)	**100**	**95**	**102**	**94**	**205**	**201**	**203**	**194**	**197**	**195**	**114**	**114**	**115**	**108**	**111**
												(9)			

FEV_1 = forced expiratory volume in 1 second; FF = fluticasone furoate (100 mcg or 200 mcg once daily); FP = fluticasone propionate (100 mcg, 250 mcg, or 500 mcg twice daily); ITT = intention-to-treat; PBO = placebo; SD = standard deviation; VI = vilanterol.
[a] Normal range was defined as 0.05 gills per litre (GI/L) to 0.55 GI/L or 0% to 5% for patients aged 12 to 16 years, and 0% to 7% for patients older than 18 years.
Source: Clinical Study Reports.[1-4,6]

TABLE 7: SUMMARY OF LUNG FUNCTIONS AT SCREENING AND BASELINE

	FFA-687 (8 weeks)				HZA-827 (12 weeks)			HZA-829 (24 weeks)			FFA-059 (24 weeks)			FFA-496 (24 weeks)	
Drug/Dosage (mcg)	**FF 100**	**FF 200**	**FP 100**	**PBO**	**FF 100**	**FF/VI 100/25**	**PBO**	**FF 200**	**FF/VI 200/25**	**FP 500**	**FF 100**	**FP 250**	**PBO**	**FF 100**	**FF 200**
ITT (N)	**100**	**95**	**102**	**94**	**205**	**201**	**203**	**194**	**197**	**195**	**114**	**114**	**115**	**108**	**111**
FEV_1, mean (SD) at screening															
Pre-bronchodilator (L)	2.28 (0.6)	2.16 (0.7)	2.24 (0.7)	2.32 (0.6)	2.17 (0.58)	2.23 (0.61)	2.28 (0.62)	2.07 (0.64)	2.02 (0.62)	2.02 (0.67)	2.27 (0.6)	2.27 (0.7)	2.22 (0.6)	1.93 (0.54)	2.01 (0.62)
% predicted (SD)	67.2 (11.3)	66.6 (12.1)	67.4 (12.8)	67.0 (11.7)	67.0 (11.4)	67.3 (11.8)	68.5 (10.5)	63.3 (12.6)	63.0 (12.3)	63.6 (12.4)	69.2 (11.0)	70.1 (12.5)	69.4 (10.0)	65.2 (12.3)	65.5 (12.4)
Post-bronchodilator (L)	2.97 (0.8)	2.77 (0.8)	2.84 (0.8)	2.95 (0.8)	2.81 (0.77)	2.83 (0.77)	2.88 (0.78)	2.66 (0.81)	2.59 (0.78)	2.60 (0.83)	2.86 (0.7)	2.82 (0.9)	2.79 (0.7)	2.52 (0.80)	2.66 (0.80)
FEV_1 reversibility, mean (SD) at screening															
Absolute (mL) (SD)	688.7 (395)	610.1 (345)	601.4 (325)	624.5 (332)	641.9 (400)	603.1 (347)	597.6 (368)	583.3 (346.3)	561.7 (367.9)	568.0 (313.1)	593.7 (291)	549.9 (338)	564.9 (319)	594.1 (385.7)	647.1 (391.7)
Per cent (%)	31.6 (18.7)	29.3 (17.1)	29.1 (17.5)	28.1 (15.8)	30.7 (19.7)	28.0 (16.0)	27.5 (18.7)	29.2 (17.0)	29.6 (19.8)	29.6 (16.4)	27.3 (15.3)	25.1 (14.5)	25.4 (13.0)	30.6 (16.1)	33.9 (20.6)
FEV_1, mean (SD) at baseline															
Pre-bronchodilator (L)	2.42 (0.6)	2.21 (0.6)	2.34 (0.7)	2.37 (0.7)	2.29 (0.6)	2.34 (0.6)	2.33 (0.6)	2.19 (0.7)	2.13 (0.7)	2.14 (0.7)	2.37 (0.6)	2.36 (0.7)	2.33 (0.7)	2.04 (0.7)	2.08 (0.7)

	FFA-687 (8 weeks)				HZA-827 (12 weeks)			HZA-829 (24 weeks)			FFA-059 (24 weeks)			FFA-496 (24 weeks)	
Drug/Dosage (mcg)	**FF 100**	**FF 200**	**FP 100**	**PBO**	**FF 100**	**FF/VI 100/25**	**PBO**	**FF 200**	**FF/VI 200/25**	**FP 500**	**FF 100**	**FP 250**	**PBO**	**FF 100**	**FF 200**
ITT (N)	**100**	**95**	**102**	**94**	**205**	**201**	**203**	**194**	**197**	**195**	**114**	**114**	**115**	**108**	**111**
% predicted (SD)	NR				70.5 (11.0)	70.6 (11.9)	70.2 (10.1)	66.7 (12.4)	66.5 (12.6)	67.6 (12.2)	72.2 (10.4)	73.0 (11.9)	72.3 (10.9)	68.4 (14.0)	67.8 (13.3)
Post-bronchodilator (L)	NR				NR			NR			NR			NR	
FEV_1 reversibility, mean (SD) at baseline															
Absolute (mL) (SD)	NR				NR			NR			NR			NR	
Per cent (%)	NR				NR			NR			NR			NR	

FEV_1 = forced expiratory volume in 1 second; FF = fluticasone furoate (100 mcg or 200 mcg once daily); FP = fluticasone propionate (100 mcg, 250 mcg, or 500 mcg twice daily); ITT = intention-to-treat; NR = not reported; PBO = placebo; SD = standard deviation; VI = vilanterol.
Source: Clinical Study Reports.[1-4,6]

3.2.3 Interventions

The included studies evaluated asthma management with once-daily administration of FF. Study FFA-687 included four different doses of FF (25 mcg, 50 mcg, 100 mcg, and 200 mcg), and Study HZA-829 evaluated FF 200 mcg; the remaining three studies evaluated a single dose of FF (100 mcg). Comparator groups varied from one study to another. Three studies included an active comparator treatment in addition to placebo; these were FP 100 mcg twice daily in Study FFA-687, FF/VI 100 mcg/25 mcg once daily in Study HZA-827, and FP 250 mcg twice daily in Study FFA-059. Study HZA-829 included two active controls, combination FF/VI 200 mcg/25 mcg daily, and FP 500 mcg. Study FFA-496 compared FF 100 mcg once daily with FF 200 mcg once daily. In all included studies, patients were allowed to use albuterol/salbutamol inhalation aerosol as a rescue medication.

3.2.4 Outcomes

The main outcome in the included studies was the change from baseline in trough evening FEV_1, which was recorded before the use of bronchodilator or the study medication dose. Two studies included a co-primary outcome considering the weighted mean FEV_1. The weighted mean was recorded over 0 to 24 hours post-dose, and included assessments after 5, 15, and 30 minutes and after 1, 2, 3, 4, 5, 12, 20, 23, and 24 hours of the administration of treatment. 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 commonly reported pulmonary function tests. [29] Considered an acceptable primary end point (although recommended as a secondary clinical end point) by Health Canada,[30] FEV_1 is widely used in clinical trials to evaluate the effectiveness of asthma treatments. Although FEV_1 is a valid measure for lung function, it seems that it has very limited evidence of a minimal clinically important difference (MCID) (APPENDIX 5). The primary outcome of the included studies was based on FEV_1 measures at eight weeks (Study FFA-687), 12 weeks (Study HZA-827), and 24 weeks (Studies HZA-829, FFA-059, FFA-496).

Secondary outcomes were recorded by patients, and included PEF, rescue-free 24-hour periods, and symptom-free 24-hour periods. PEF is defined as "the maximum flow achieved during an expiration delivered with maximal force starting from the level of maximal lung inflation."[31] It can be measured using a mechanical peak flow meter, in which case patients may be asked to record their PEF values in diaries. There is strong evidence, however, that these diaries are often unreliable among asthmatic patients, particularly children.[32-34] Alternatively, PEF may be measured using electronic peak flow meters, 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. Some trialists have used a value of 25 L/min as an MCID for PEF values among patients with asthma.[35,36]

Three studies (HZA-827, HZA-829, and FFA-059) used the Asthma Quality of Life Questionnaire for 12 years and older (AQLQ +12), which is a patient-reported, disease-specific, health-related quality of life measure. 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 seven-point scale that 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 to the questions in the respective domains. Patients recall their relevant experiences during the previous two weeks. No study appears to have formally established the MCID for AQLQ +12, although given the significant overlap between the AQLQ +12 and the original Asthma Quality of Life Questionnaire (AQLQ), researchers consider a cut-point of 0.5 to indicate a clinically important difference (APPENDIX 5).[37-39]

3.2.5 Statistical Analysis

Study FFA-867 and FFA-059 were designed to have statistical power of 90% and 94%, respectively, to detect a difference of 200 mL in pairwise comparisons of change from baseline in trough FEV_1 between any active dose and placebo. Both Studies HZA-827 and HZA-829 included two co-primary outcomes, and their sample sizes ensured respective overall power of 83% and 92%, respectively, to detect treatment differences for both primary end points. In addition, Study HZA-829 was designed to have 80% power to test the non-inferiority of FF 200 mcg once daily relative to FP 500 mcg twice daily with a non-inferiority bound of –125 mL of change from baseline in clinic visit trough FEV_1. The manufacturer did not provide empirical evidence to support the selected inferiority margin; however, the clinical expert consulted on this review pointed out that this value was an appropriate non-inferiority threshold. This comparison was made on the per-protocol (PP) population as well as on the intention-to-treat (ITT) population.

Study FFA-496 did not report on power estimation; instead it was reported that the sample size would ensure that the half-width of the 95% confidence interval (CI) was no larger than 110.1 mL, providing an estimated mean treatment difference between treatment groups in change from baseline in FEV_1 at the end of the 24-week treatment period.

The included studies accounted for multiplicity across the key outcomes by using a step-down, closed testing procedure. In this strategy, the primary treatment comparison was required to be significant at the 0.05 level for the primary end point in order to infer on the secondary end points; inference for a test in the pre-defined hierarchy of secondary end points is dependent upon statistical significance having been achieved for the previous comparison in the hierarchy of secondary end points. If a given statistical test failed to reject the null hypothesis of no treatment difference at the significance level of 0.05, then all tests lower down in the hierarchy were interpreted as descriptive only. Of note, the included studies used the 0.05 significance level for all outcomes, even for the co-primary outcomes in Studies HZA-827 and HZA-829.

Outcome analyses were conducted using mixed or analysis of covariance (ANCOVA) models, allowing for effects due to baseline outcome value, region, sex, age, visit, and treatment group. Missing data were imputed by carrying forward the last available observation.

a) Analysis Populations

The included studies shared dataset definitions and included the following:

- **Total population** comprised all patients screened who had a record on the study database. This population was used for the tabulation of reasons for withdrawal before randomization.
- **Modified intention-to-treat (mITT) population** comprised all patients randomized to treatment who received at least one dose of study medication. Randomized patients were assumed to have received study medication unless definitive evidence to the contrary existed. This constituted the primary population for all analyses of efficacy measures and safety measures (excluding urinary cortisol analyses). Outcomes were reported according to the randomized treatment allocation.
- **Per-protocol population** consisted of all patients in the ITT population who did not have any full protocol deviations. Protocol deviations could be either full or partial. Patients with only partial deviations were considered part of the PP population, but their data were excluded from the date of their deviation onwards. The decision to exclude a patient or part of their data from the PP population was made prior to breaking the blind. This population was used only for confirmatory analysis of the primary efficacy end point and the nominated powered secondary efficacy end point.

3.3 Patient Disposition

Patient disposition is summarized in Table 8. Study completion was not consistent across trials, and varied among treatment arms within each study. In Studies HZA-827 and FFA-059, placebo groups had the highest rates of premature withdrawal of 26% and 35%, respectively. In Study FFA-687, the placebo group had the highest rate of premature withdrawal (19%), but this rate was similar to that of the FP 100 mcg group (18%). Premature withdrawals among the FF 100 mcg groups ranged from 10% in Study HZA-827 to 19% in Study FFA-059. Similarly, FF 200 mcg groups had premature withdrawal rates ranging from 9% in Study FFA-687 to 25% in Study HZA-829.

Protocol violation ranged from 8% to 23%; the highest rates were reported in Study FFA-059 (15% to 23%) and in Study FFA-496 (16% to 23%), and the lowest rates were reported in Study FFA-687 (8% to 13%). Withdrawal due to lack of efficacy was the highest in the three placebo groups, ranging from 15% in Study FFA-567 to 20% in Study FFA-059.

3.4 Exposure to Study Treatments

Exposure to study treatments is presented in Table 9 in different time intervals. In Studies FFA-687, HZA-827, and FFA-059, patients who were treated with placebo had the highest rates of treatment exposure of ≤ 4 weeks. The higher rates of short exposure are concordant with the observation of premature withdrawals in the placebo groups. In Studies HZA-827 and FFA-059, placebo groups had the highest rates of short exposure (15% and 11%, respectively). In Study FFA-687, placebo group had the highest rate of short exposure (14%), but this rate was similar to the premature withdrawal rate of the FP 100 mcg group (13%).

TABLE 8: PATIENT DISPOSITION

	FFA-687 (8 weeks)				HZA-827 (12 weeks)			HZA-829 (24 weeks)			FFA-059 (24 weeks)			FFA-496 (24 weeks)	
Drug/Dosage (mcg)	**FF 100**	**FF 200**	**FP 100**	**PBO**	**FF 100**	**FF/VI 100/25**	**PBO**	**FF 200**	**FF/VI 200/25**	**FP 500**	**FF 100**	**FP 250**	**PBO**	**FF 100**	**FF 200**
Screened, N	1,459				1,110			1,206			1,036			500	
Screen failure, N (%)	NR				379 (34)			478 (40)			529 (51)			150 (30)	
Run-in, N (%)	NR				731 (66)			728 (60)			507 (49)			350 (70)	
Run-in failure, N (%)	NR				120 (11)			141 (12)			157 (15)			111 (22)	
Randomized, N	601				610			587			349			239	
	111	95	102	94	205	202	203	194	197	161	116	116	117	120	119
ITT, N (%)	110 (> 99)	95 (100)	102 (100)	94 (100)	205 (100)	201 (> 99)	203 (100)	194 (100)	197 (100)	195 (> 99)	114 (98)	114 (98)	115 (98)	108 (90)	111 (93)
PP, N (%)	97 (87)	87 (92)	92 (90)	79 (84)	184 (90)	181 (90)	181 (89)	175 (90)	172 (87)	168 (86)	91 (78)	89 (77)	100 (85)	92 (77)	100 (84)
Urinary cortisol, N (%)	76 (68)	69 (73)	70 (69)	66 (70)	156 (76)	153 (76)	136 (67)	126 (65)	140 (71)	123 (63)	71 (61)	73 (63)	53 (45)	68 (57)	80 (67)
Study completion status based on the ITT population															
Completed, N (%)	98 (89)	86 (91)	84 (82)	76 (81)	185 (90)	179 (89)	151 (74)	146 (75)	169 (86)	161 (83)	92 (81)	88 (77)	75 (65)	100 (84)	104 (87)
Premature withdrawal, N (%)	12 (11)	9 (9)	18 (18)	18 (19)	20 (10)	22 (11)	52 (26)	48 (25)	28 (14)	34 (17)	22 (19)	26 (23)	40 (35)	12 (11)	11 (10)
Primary reason for withdrawal, N (%)															
AEs	2 (2)	1 (1)	2 (2)	0	0	2 (< 1)	1 (< 1)	3 (2)	7 (4)	2 (1)	2 (2)	3 (3)	2 (2)	2 (2)	2 (2)
Lack of efficacy	6 (5)	6 (6)	11 (11)	14 (15)	6 (3)	7 (3)	32 (16)	21 (11)	6 (3)	18 (9)	15 (13)	14 (12)	23 (20)	2 (2)	1 (< 1)
Protocol deviation	2 (2)	1 (1)	0	1 (1)	0	2 (< 1)	7 (3)	5 (3)	3 (2)	5 (3)	2 (2)	3 (3)	1 (< 1)	2 (2)	3 (3)
Consent withdrawal	1 (1)	0	1 (1)	3 (3)	6 (3)	3 (1)	6 (3)	13 (7)	4 (2)	7 (4)	3 (3)	3 (3)	10 (9)	4 (3)	3 (3)

AE = adverse event; FF = fluticasone furoate (100 mcg or 200 mcg once daily); FP = fluticasone propionate (100 mcg, 250 mcg, or 500 mcg twice daily); ITT = intention-to-treat; PBO = placebo; PP = per-protocol; VI = vilanterol.
Source: Clinical Study Reports.[1-4,6]

TABLE 9: SUMMARY OF EXPOSURE TO STUDY TREATMENTS

	FFA-687 (8 weeks)				HZA-827 (12 weeks)			HZA-829 (24 weeks)			FFA-059 (24 weeks)			FFA-496 (24 weeks)	
Drug/Dosage (mcg)	**FF 100**	**FF 200**	**FP 100**	**PBO**	**FF 100**	**FF/VI 100/25**	**PBO**	**FF 200**	**FF/VI 200/25**	**FP 500**	**FF 100**	**FP 250**	**PBO**	**FF 100**	**FF 200**
Total, N	**110**	**95**	**102**	**94**	**205**	**201**	**203**	**194**	**197**	**195**	**114**	**114**	**115**	**108**	**111**
NDPI Exposure (days)															
Mean, days (SD)	54 (10)	53 (12)	51 (14)	50 (16)	80.6 (14)	80.8 (13)	71.7 (25)	144.7 (49)	156.7 (34.8)	149.4 (46.9)	149 (43)	147 (46)	132 (56)	159.8 (29.7)	160.6 (29.2)
Range, n (%)															
≤ 28 days	5 (5)	6 (6)	13 (13)	14 (14)	6 (3)	4 (2)	30 (15)	16 (8)	7 (4)	15 (8)	5 (4)	6 (5)	12 (11)	3 (3)	1 (< 1)
29 to 56 days	45 (42)	37 (39)	36 (36)	31 (33)	7 (3)	8 (4)	9 (4)	6 (3)	2 (1)	6 (3)				0	2 (2)
≥ 57 days	59 (54)	52 (55)	52 (51)	49 (52)											
57 to 84 days					77 (38)	73 (36)	74 (37)	4 (2)	2 (1)	5 (3)				1 (< 1)	3 (3)
≥ 85 days					115 (56)	116 (58)	88 (44)								
141 to 168 days								75 (39)	86 (44)	81 (42)	76 (67)	80 (70)	59 (52)	57 (53)	55 (50)
≥ 169 days								75 (39)	87 (44)	84 (43)	17 (15)	14 (12)	17 (15)	40 (37)	45 (41)
DISKUS/ACCUHALER[a] Exposure (days)															
Mean, days (SD)	54 (10)	53 (12)	51 (14)	50 (16)				145.1 (49.3)	157.2 (34.8)	150.0 (46.8)	150 (43)	148 (46)	133 (56)		
Range, n (%)															
≤ 28 days	5 (5)	6 (6)	10 (10)	14 (14)				13 (7)	7 (4)	14 (7)	5 (4)	5 (4)	11 (10)		
29 to 56 days	43 (40)	37 (39)	39 (39)	31 (33)				8 (4)	2 (1)	5 (3)					
≥ 57 days	61 (56)	52 (55)	52 (51)	49 (52)											
141 to 168 days								71 (37)	74 (38)	67 (34)	38 (34)	45 (39)	29 (25)		
≥ 169 days								83 (43)	99 (51)	99 (51)	55 (49)	49 (43)	48 (42)		

FF = fluticasone furoate (100 mcg or 200 mcg once daily); FP = fluticasone propionate (100 mcg, 250 mcg, or 500 mcg twice daily); ITT = intention-to-treat; NDPI = novel dry powder inhaler (dispenser used to deliver FF); PBO = placebo; SD = standard deviation; VI = vilanterol (25 mcg once daily).

[a] DISKUS/ACCUHALER is a dispenser used to deliver FP.

Source: Clinical Study Reports.[1-4,6]

3.5 Critical Appraisal

3.5.1 Internal Validity

Only Study HZA-829 compared the non-inferiority of FF 200 mcg once daily with FP 500 mcg twice daily. The manufacturer did not provide empirical evidence to support the selected inferiority margin; however, the clinical expert consulted on this review pointed out that this value was an appropriate non-inferiority threshold. Study HZA-829 included patients who had been treated with high-dose ICSs, which might indicate that these patients had more severe asthma than patients included in the other trials. Therefore, the results of non-inferiority testing in Study HZA-829 might not be generalizable to all asthma patients, especially to patients with milder forms of asthma. In the remaining four studies, the objectives were not to show non-inferiority or equivalence between FF and FP. Hence, it cannot necessarily be concluded from the lack of statistically significant differences between FF and FP that the two treatments are equivalent or non-inferior to each other.

The primary analyses in the included studies were not true ITT, but modified ITT; more than 10% of patients were not included in the ITT analyses of Study FFA-496, which could have affected the study results. Furthermore, up to 23% of patients in the included studies had one or more major protocol deviations and were excluded from the efficacy dataset. Therefore, the excluded data certainly could have, and most likely did, affect the study results; however, the direction and magnitude of this effect could not be estimated. The overall proportion of patients with major protocol violations appeared to be similar between the active comparator groups.

Multiplicity was not properly accounted for in the included studies. The statistical testing continued with the next outcome in the hierarchy if at least one null hypothesis of the two (or three) treatment comparisons was rejected; otherwise, the sequential testing procedures were stopped for inferential purposes. However, the statistical testing was based on a 0.05 significance level, and this value was used for all outcomes including the co-primary outcomes in Studies HZA-827 and HZA-829. A true account for multiplicity would have divided the significance level value on the number of tests or outcomes.

Limited comparisons between FF and FP can be adequately assessed, as only one trial conducted a non-inferiority analysis between these two corticosteroids. Any between-group differences cannot be properly evaluated in the other trials, as no statistical analysis was completed. Statistical comparisons for outcomes reported to be relevant by patients were not completed and the studies were not adequately powered to address these outcomes.

The included studies provided no data on the quality assessment of lung function measurements using spirometry (for example, any violations in withholding bronchodilators before FEV_1 assessments). It therefore remains uncertain whether invalid spirometric measurements would have affected the efficacy assessments, although bias due to such invalid measurements is perhaps unlikely, as there is little reason to believe that they would have occurred preferentially in one arm compared with another.

All included studies were DB. However, placebo groups showed the highest rates of premature discontinuation, withdrawal due to lack of efficacy, and short duration exposure, which indicate that blinding might be unconcealed in these groups; in addition, these withdrawals probably overestimated the treatment effect. Most of the outcomes in the included studies were reported by patients; therefore, outcome assessment might be biased in favour of the active treatments. A patient's knowledge of his/her treatment might have affected the effort he or she put in the spirometric testing too, which might potentially raise uncertainty around the FEV_1 comparisons versus placebo.

3.5.2 External Validity

The included studies recruited asthma patients with a wide range of asthma severity. Although not explicitly specified, asthma severity could be deduced from pre-study asthma medication. However, only ≤ 8% of the included patients had had their asthma diagnosed within one year of study initiation; therefore, the results might not be generalizable to newly diagnosed asthma patients. Furthermore, only 1% to 16% of patients were younger than 18 years; therefore, the findings from the included studies might not be generalizable to patients younger than 18 years.

Baseline asthma severity was evaluated by FEV_1 and the asthma reversibility test; the pre-bronchodilator per cent predicted FEV_1 ranged from 63% to 70%, and FEV_1 reversibility ranged from 13% to 21%. These values indicate that the included patients might have been suboptimally treated for their asthma. Therefore, results might be biased in favour of the active treatment groups, because patients in these groups would have their treatment dose optimized while placebo patients would have their suboptimal active ICS switched to placebo.

The short duration of trials, eight weeks to 24 weeks, is inadequate to assess the long-term efficacy and safety of a medication routinely used for a chronic condition such as asthma. As well, generalizability of the patient population and interventions is limited, as LABA use in asthma populations would be more routinely seen than was shown in these trials.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 3). See APPENDIX 4 for detailed efficacy data.

3.6.1 Incidence of Acute Exacerbations of Asthma

Results of acute exacerbations of asthma are summarized in Table 12. Overall, the incidence of severe asthma exacerbations was low, ranging from 0% to 4% in four studies (FFA-687, HZA-827, HZA-829, and FFA-059). In Study FFA-496, incidence rates were relatively higher than in the other studies, ranging from 12% to 13%. There was no obvious trend or differences between the evaluated treatments or placebo. Statistical comparisons between treatments were not conducted or reported.

3.6.2 Number of Asthma Symptom-Free 24-hour Periods

Results of asthma symptom-free periods are summarized in Table 13. Change from baseline results showed that placebo was associated with an increase of 11.3% to 18.0% of symptom-free 24-hour periods; FF 100 mcg was associated with a 16.6% to 37.6% increase; FF 200 mcg was associated with a 20.4% to 32.3% increase; and FP was associated with a 19% to 34% increase. The highest percentage of symptom-free periods for the active treatments was recorded in Study FFA-687 after eight weeks of treatment, and the lowest percentages were recorded in Studies HZA-829, FFA-059, and FFA-496 after 24 weeks of treatment.

Differences in change from baseline versus placebo varied from one study to another. After eight weeks in Study FFA-687, all active treatments were associated with a statistically significantly larger increase in symptom-free periods; least squares (LS) mean differences versus placebo (*P* values) were 20.2% (< 0.001), 13.2 (0.004), and 14.9 (< 0.001) for FF 100 mcg, FF 200 mcg, and FP 100 mcg, respectively. Study HZA-827 showed that, after 12 weeks of treatment, FF 100 mcg was associated with 5.8% more LS mean symptom-free periods than placebo, but this difference was not statistically significant. Study FFA-059 showed that after 24 weeks of treatment, both FF 100 mcg and FP 250 mcg were associated with

statistically significantly larger LS mean increases in symptom-free periods compared with placebo (8.9% [*P* = 0.025] and 8.8% [*P* = 0.025], respectively).

Statistical testing of the differences in symptom-free periods between FF and FP was not conducted or reported in the included studies. Study HZA-827 and Studies HZA-827 and HZA-829 showed that FF 100 mcg was associated with statistically fewer symptom-free periods compared with the combination therapy of FF/VI; the LS mean differences (*P* values) were –12.1% (0.001) and –8.4 (0.01) in the two studies, respectively. Study FFA-496 reported that FF 100 mcg was associated with a non-significant 2.1% (CI, –9.9% to 5.7%) smaller increase in symptom-free periods than FF 200 mcg.

3.6.3 Incidence of Dyspnea

Dyspnea was not an outcome in the included studies.

3.6.4 Nocturnal Awakening

Sleep disruption was not an outcome in the included studies. However, a nighttime asthma symptom score was part of protocol-defined outcomes, and is supposed to capture awakening and sleep disturbances; however, those results were not reported.

3.6.5 Change in Pulmonary Function (FEV_1 and PEF)

a) FEV_1

Results of absolute volume of evening trough FEV_1 are summarized in Table 14. Change from baseline results showed that placebo was associated with an increase that ranged from 0.02 L (Study FFA-059) to 0.20 L (Study HZA-827); FF 100 mcg was associated with a 0.16 L (Study FFA-059) to 0.34 L (Study FFA-687) increase; FF 200 mcg was associated with a 0.28 L (Study FFA-796) to 0.37 L (Study FFA-687) increase; and FP was associated with a 0.16 L (Study FFA-059) to 0.24 L (Study FFA-687) increase. The highest FEV_1 volume for the active treatments were reported in Study FFA-687 after eight weeks of treatment, and the lowest rates were recorded in Studies HZA-829, FFA-059, and FFA-496 after 24 weeks of treatment.

The LS mean differences in change from baseline versus placebo ranged from 0.11 L to 0.20 L. After eight weeks in Study FFA-687, FF 100 mcg and 200 mcg were associated with a statistically significantly larger increase in FEV_1 volume; LS mean differences versus placebo (*P* values) were 0.20 L (< 0.001) and 0.23 L (< 0.001) for FF 100 mcg and FF 200 mcg, respectively. The LS mean difference between FP 100 mcg and placebo was not statistically significant (0.11 L [0.074]). Study HZA-827 showed that, after 12 weeks of treatment, FF 100 mcg was associated with 0.136 L (0.002) larger LS mean increase in FEV_1 volume than placebo. Study FFA-059 showed that after 24 weeks of treatment, both FF 100 mcg and FP 250 mcg were associated with statistically significantly larger LS mean increase in FEV_1 volume of 0.15 L (0.009) and 0.15 L (0.011) than placebo, respectively.

Study HZA-829 included non-inferiority testing of the differences between FF 200 mcg and FP 500 mcg. Results showed that FF 200 mcg was associated with a similar FEV_1 volume; LS mean difference (CI) was 0.018 L (–0.066 L to 0.102 L). This difference achieved the non-inferiority definition of a 0.125 L limit, and was consistent in the mITT and PP analyses. Study HZA-829 showed that combination FF/VI was associated with a statistically larger increase in FEV_1 volume than FF 100 mcg alone; the LS mean difference (*P* value) was 0.19 L (< 0.001). Study FFA-496 showed that FF 100 mcg was associated with a non-significant 0.077 L (CI, –0.192 L to 0.039 L) smaller increase in FEV_1 volume than FF 200 mcg.

b) Weighted Mean FEV_1 (0 to 24 Hours)

The weighted mean FEV_1 results are summarized in Table 15. Study HZA-827 showed that both FF 100 mcg and combination FF/VI were associated with a larger increase than placebo in change from baseline in terms of weighted LS mean FEV_1; differences (*P* values) were 0.186 L (0.003) and 0.302 L (< 0.001) for the two groups, respectively. No statistically significant difference was observed between combination FF 100 mcg/VI 25 mcg and FF 100 mcg treatments. Study HZA-829 reported a statistically significant difference between FF 200 mcg and combination FF 200 mcg/VI 25 mcg favouring the combination therapy; LS mean difference (*P* value) was 0.14 L (0.048). Difference between FF 200 mcg and FP 500 mcg was not reported.

c) Evening PEF

Results of evening PEF volume are summarized in Table 16. Patients treated with placebo in Studies FFA-059 and HZA-827 experienced a decrease in PEF of 1.3 L/min to 1.8 L/min, respectively; placebo patients in Study FFA-687 had a PEF increase of 9.6 L/min. Change from baseline in the active treatments showed that FF 100 mcg was associated with an increase ranging from 1.5 L/min in Study FFA-059 to 25.7 L/min in Study FFA-687; FF 200 mcg was associated with a 7.2 L/min (Study FFA-496) to 31.3 L/min (Study FFA-687) increase; and FP was associated with a 4.3 L/min increase (Study FFA-059) to 24.4 L/min increase (Study FFA-687). The higher flow rates for the active treatment groups were recorded in Study FFA-687 after eight weeks of treatment, and the lowest rates were recorded in Studies FFA-059 and FFA-496 after 24 weeks of treatment.

The LS mean differences in change from baseline versus placebo varied from one study to another. After eight weeks in Study FFA-687, all active treatments were associated with statistically significantly larger LS mean increases in PEF; differences versus placebo (*P* values) were 16 L/min (0.005), 21.7 (< 0.001) and 14.9 (0.011) for FF 100 mcg, FF 200 mcg, and FP 100 mcg, respectively. Study HZA-827 showed that, after 12 weeks of treatment, FF 100 mcg was associated with a 15.9 L/min (< 0.001) larger LS mean increase in PEF than placebo. Study FFA-059 showed that after 24 weeks of treatment, neither FF 100 mcg nor FP 250 mcg were associated with statistically significantly larger LS mean increases in PEF; differences (*P* values) were 2.8 L/min (0.564) and 5.5 L/min (0.248), respectively.

Statistical testing of the differences between FF and FP was not conducted or reported for PEF. Study HZA-827 and HZA-829 showed that combination FF/VI was associated with statistically larger LS mean increase in PEF than in FF 100 mcg alone; the LS mean differences (*P* values) were 12.3 L/min (0.001) and 30.7 L/min (< 0.001) in the two studies, respectively. Study FFA-496 showed that FF 100 mcg was associated with a non-significant 1.3L/min (CI, -7.8 to 10.4) smaller LS mean increase in PEF than FF 200 mcg.

Morning PEF results are summarized in Table 17; they were consistent with the evening PEF results.

3.6.6 Quality of Life

Total scores of AQLQ +12 are summarized in Table 18, and the results by domain are presented in Table 19 (Activity Limitation), Table 20 (Symptoms), Table 21 (Emotional Function), and Table 22 (Environmental Stimuli).

LS mean differences in total AQLQ + 12 score change from baseline versus placebo were not consistent across the three studies that reported this outcome. In Study FFA-687, FF 100 mcg was associated with a numerically larger LS mean increase in total score than placebo, but this difference was not statistically significant; difference (*P* value) was 0.15 (0.073). In contrast, Study FFA-059 showed that FF 100 mcg

was associated with a statistically significant larger LS mean increase in AQLQ + 12 total score than placebo of 0.33 (0.007), but FP 250 mcg did not statistically differ from placebo (LS mean difference of 0.16; *P* = 0.185). These differences did not reach the MCID of 0.5.

Statistical testing of the differences between FF and FP was not conducted or reported for AQLQ + 12. Study HZA-827 and HZA-829 did not show statistically significant differences in AQLQ + 12 scores between combination FF/VI and FF 100 mcg alone; the LS mean differences (*P* values) were 0.15 (0.059) and 0.05 (0.59) in the two studies, respectively. Differences between treatments were not reported for the individual AQLQ + 12 domains.

3.6.7 Rescue-Free 24-hour Periods

Results of rescue-free periods are summarized in Table 23. Change from baseline results showed that placebo was associated with an increase of 7% to 22% of rescue-free 24-hour periods; FF 100 mcg was associated with a 21% to 41% increase; FF 200 mcg was associated with a 23% to 32% increase; and FP was associated with a 24% to 36% increase. The highest percentage of rescue-free periods for the active treatments were recorded in Study FFA-687 after eight weeks of treatment, and the lowest rates were recorded in Studies FFA-059 and FFA-496 after 24 weeks of treatment.

LS mean differences in change from baseline versus placebo varied from 8.7% to 18.9%. After eight weeks in Study FFA-687, all active treatments were associated with statistically significantly larger LS mean increases in rescue-free periods; differences versus placebo (*P* values) were 18.9% (< 0.001), 10.1 (0.031), and 13.7 (0.003) for FF 100 mcg, FF 200 mcg, and FP 100 mcg, respectively. Study HZA-827 showed that, after 12 weeks of treatment, FF 100 mcg was associated with 8.7% (0.007) more rescue-free periods than placebo. Study FFA-059 showed that after 24 weeks of treatment, both FF 100 mcg and FP 250 mcg were associated with statistically significantly larger LS mean increases in rescue-free periods of 14.8% (< 0.001) and 17.9% (< 0.001), respectively.

Statistical testing of the differences between FF and FP was not conducted or reported in the included studies. Study HZA-827 and HZA-829 showed that combination FF/VI was associated with statistically larger LS mean increases in rescue-free periods than FF 100 mcg alone; the differences (*P* values) were 10.6% (< 0.001) and –11.7 (< 0.001) in the two studies, respectively. Study FFA-496 showed that FF 100 mcg was associated with a non-significant 1.8% (CI, –10.3% to 6.7%) lower increase in rescue-free periods than FF 200 mcg.

3.6.8 Other Efficacy Outcomes

a) Incidence of Missing Work/School Days

This outcome was not reported in the included studies.

b) Incidence of Hospitalizations, Emergency Room Visits, or MD Visits

None of the included patients reported unscheduled medical visits related to asthma in Studies HZA-827, HZA-829, FFA-059, and FFA-496. Study FFA-687 did not report this outcome.

c) Ease of Use of, and Adherence to, Treatment

An adequate assessment of ease of use of, or adherence to, treatment was not reported. Study HZA-827 and FFA-496 reported that 94% to 96% of the included patients used their inhalers correctly at baseline, and that 98% to 100% of patients used them correctly at the subsequent visits (Table 25).

TABLE 10: KEY EFFICACY OUTCOMES

	FFA-687 (8 wks)				HZA-827 (12 wks)			HZA-829 (24 wks)			FFA-059 (24 wks)			FFA-496 (24 wks)	
Drug/Dosage (mcg)	**FF 100**	**FF 200**	**FP 100**	**PBO**	**FF 100**	**FF/VI 100/25**	**PBO**	**FF 200**	**FF/VI 200/25**	**FP 500**	**FF 100**	**FP 250**	**PBO**	**FF 100**	**FF 200**
Total, N	**110**	**95**	**102**	**94**	**205**	**201**	**203**	**194**	**197**	**195**	**114**	**114**	**115**	**108**	**111**
Severe asthma exacerbations															
n (%)	3 (3)	1 (1)	2 (2)	0	4 (2)	1 (< 1)	9 (4)	6 (3)	0	2 (1)	2 (2)	2 (2)	4 (3)	14 (13)	13 (12)
FF vs. other groups	NR	NR	NA	NA	NR	NA	NA	NR	NA	NA	NR	NA	NA	NR	NA
% of symptom-free 24 hour periods															
LS mean change from baseline, mean (SD)	38.7 (3.0)	31.7 (3.2)	33.3 (3.1)	18.4 (3.2)	20.4 (2.1)	32.5 (2.1)	14.6 (2.2)	21.0 (2.32)	29.3 (2.29)	24.5 (2.31)	19.3 (2.8)	19.2 (2.8)	10.4 (2.8)	17.5 (2.80)	19.6 (2.79)
LS mean difference vs. PBO; *P* value	20.2; 0.001	13.2; 0.004	14.9; 0.001	NA	5.8; **0.055**	18.0; < 0.001	NA	NA	NA	NA	8.9 0.025	8.8 0.025	NA	NA	
FF vs. active arms (95% CI) or *P* value	NR	NA			NA	–12.1; 0.001	NA	NA	–8.4; 0.01	NR	NR	NA		–2.1 (–9.9, 5.7)	
Evening trough FEV_1 (Absolute volume), L															
LS mean change from baseline, mean (SD)	0.34 (0.04)	0.37 (0.04)	0.24 (0.04)	0.14 (0.04)	0.33 (0.03)	0.37 (0.03)	0.20 (0.03)	0.20 (0.03)	0.39 (0.03)	0.18 (0.03)	0.16 (0.04)	0.16 (0.04)	0.02 (0.04)	0.21 (0.04)	0.28 (0.04)
LS mean difference vs. PBO; *P* value	0.20; 0.001	0.23; 0.001	0.11; 0.074	NA	0.136; 0.002	0.172; 0.001	NA	NA	NA	NA	0.15; 0.009	0.15; 0.011	NA		
FF vs. active arms (95% CI), *P* value	NR	NR	NA	NA	–0.04; 0.405	NA	NA	NA	–0.19; < 0.001	–0.018; > 0.05	NR	NA	NA	0.077 (–0.039, 0.192)	
Evening PEF, (L/min)															
LS mean change from baseline, mean (SD)	25.7 (3.90)	31.3 (4.20)	24.4 (4.04)	9.6 (4.21)	14.1 (2.34)	26.4 (2.35)	–1.8 (2.36)	9.1 (2.98)	39.8 (2.93)	13.6 (2.96)	1.5 (3.39)	4.3 (3.4)	–1.3 (3.36)	5.9 (3.26)	7.2 (3.25)
LS mean difference vs. PBO; *P* value	16.1; 0.005	21.7; 0.001	14.9; 0.011	NA	15.9; < 0.001	28.2; < 0.001	NA	NA	2.8; 0.564	5.5; 0.248	NA			NA	

	FFA-687 (8 wks)		HZA-827 (12 wks)			HZA-829 (24 wks)			FFA-059 (24 wks)			FFA-496 (24 wks)
FF vs. active arms (95% CI), *P* value	NR	NA	–12.3; 0.001	NA		NA	30.7; < 0.001	NR	NR	NA		–1.3 (–10.4, 7.8)
AQLQ +12 Total Score												
LS mean change from baseline, mean (SD)			0.76 (0.06)	0.91 (0.06)	0.61 (0.06)	0.88 (0.07)	0.93 (0.07)	0.90 (0.07)	0.84 (0.08)	0.68 (0.08)	0.51 (0.09)	
LS mean difference vs. PBO; *P* value			0.15; 0.073	0.30; < 0.001	NA	NA			0.33; 0.007	0.16; 0.185	NA	
FF vs. active arms (95% CI), *P* value			–0.15; 0.059	NA		NA	0.05; 0.59	NR	NR	NA		

AQLQ +12 = Asthma Quality of Life Questionnaire 12 years and older; FEV_1 = forced expiratory volume in one second; FF = fluticasone furoate; FP = fluticasone propionate; LS = least squares; NA = not applicable; NR = not reported; PEF = peak expiratory flow; PBO = placebo; SD = standard deviation; vs = versus; VI = vilanterol; wks = weeks.
Source: Clinical Study Reports.[1-6]

3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). See Table 11 for detailed harms data.

3.7.1 Adverse Events

The included studies showed that 21% to 63% of the included patients experienced at least one adverse event (AE). Placebo groups were associated with the lowest rates of AEs compared with the active treatment groups in Studies FFA-687, HZA-827, and FFA-059. Comparisons among studies revealed that Study HZA-827 had the lowest rate of AEs (21% to 29%), while Study FFA-496 had the highest rate of AEs (59% to 63%).

The most common individual AEs were bronchitis (0% to 12%), headache (4% to 13%), and nasopharyngitis (1% to 20%). There was no clear trend of association between these AEs and particular treatment groups.

3.7.2 Serious Adverse Events

Serious adverse events (SAEs) were relatively rare, and the percentage of patients with at least one SAE ranged from 0% to 3%. Study FFA-496 had the highest rate of AEs (3%) registered for both FF groups (100 mcg and 200 mcg).

3.7.3 Withdrawals Due to Adverse Events

Withdrawals due to adverse events (WDAEs) ranged from 0% to 4%, but there was no clear association between their occurrence and the different treatment groups.

3.7.4 Mortality

No deaths were reported in the included studies.

3.7.5 Notable Harms

The included studies did not report on growth rate or adrenal suppression. Infections and infestations (System Organ Class Preferred Term) were frequent, ranging from 6% to 41%. The lowest rates were recorded in Studies FFA-687 (6% to 14%) and HZA-827 (11% to 17%), while the highest rates were recorded in Studies HZA-829 (30% to 36%) and FFA-496 (40% and 41%). These AEs were reported more often in the FF 100 mcg group compared with FP groups, but the difference was not evident when FF 200 mcg was considered.

TABLE 11: HARMS

	FFA-687 (8 weeks)				HZA-827 (12 weeks)			HZA-829 (24 weeks)			FFA-059 (24 weeks)			FFA-496 (24 weeks)	
Drug/Dosage (mcg)	**FF 100**	**FF 200**	**FP 100**	**PBO**	**FF 100**	**FF/VI 100/25**	**PBO**	**FF 200**	**FF/VI 200/25**	**FP 500**	**FF 100**	**FP 250**	**PBO**	**FF 100**	**FF 200**
Total, N	**110**	**95**	**102**	**94**	**205**	**201**	**203**	**194**	**197**	**195**	**114**	**114**	**115**	**119**	**119**
AEs															
Patients with > 0 AEs, N (%)	35 (32)	27 (28)	35 (34)	24 (26)	52 (25)	59 (29)	43 (21)	90 (46)	92 (47)	97 (50)	60 (53)	48 (42)	46 (40)	70 (59)	75 (63)
Most common AEs[a]															
Bronchitis	1 (1)	1 (1)	2 (2)	1 (1)	0	1 (< 1)	3 (1)	6 (3)	7 (4)	6 (3)	8 (7)	4 (4)	7 (6)	14 (12)	8 (7)
Headache	12 (11)	5 (5)	12 (12)	10 (11)	9 (4)	10 (5)	8 (4)	13 (7)	11 (6)	15 (8)	7 (6)	7 (6)	5 (4)	12 (10)	15 (13)
Nasopharyngitis	4 (4)	3 (3)	2 (2)	1 (1)	14 (7)	20 (10)	15 (7)	27 (14)	25 (13)	39 (20)	9 (8)	4 (4)	6 (5)	14 (12)	15 (13)
URTI	3 (3)	0	1 (< 1)	0	4 (2)	3 (1)	0	7 (4)	7 (4)	7 (4)	7 (6)	6 (5)	6 (5)	2 (2)	7 (6)
SAEs															
Patients with > 0 SAEs, N (%)	1 (1)	0	2 (2)	0	1 (< 1)	0	0	1 (< 1)	6 (3)	2 (1)	4	1	2	3 (3)	4 (3)
WDAEs															
WDAEs, N (%)	2 (2)	1 (1)	2 (2)	0	0	2 (< 1)	1 (< 1)	3 (2)	7 (4)	2 (1)	3 (3)[b]	3 (3)[b]	2 (2)[b]	2 (2)	2 (2)
Deaths															
Number of deaths, N (%)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Notable harms															
Growth rate	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Infections and infestations	15 (14)	11 (12)	9 (9)	6 (6)	31 (15)	34 (17)	22 (11)	61 (31)	59 (30)	70 (36)	47 (41)	21 (18)	31 (27)	49 (41)	48 (40)
Adrenal suppression	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

AE = adverse event; FF = fluticasone furoate (100 mcg or 200 mcg once daily); FP = fluticasone propionate (100 mcg twice daily); NR = not reported; PBO = placebo; SAE = serious adverse event; URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse event; VI = vilanterol (25 mcg).

[a] Occurring in > 5% of patients.

[b] The manufacturer reported both permanent discontinuation and withdrawal from study as one outcome.

Source: Clinical Study Reports.[1-6]

4. DISCUSSION

4.1 Summary of Available Evidence

Five multicentre, active-controlled, DB, parallel-group RCTs met the criteria for inclusion in the systematic review. The included studies evaluated FF by comparing its efficacy with FP, combination FF/VI, and/or placebo. One study evaluated the non-inferiority of FF 200 mcg once daily with FP 500 mcg twice daily. Study duration was eight weeks in one study, 12 weeks in two studies, and 24 weeks in three studies. The patient populations enrolled in these trials were consistent with the Health Canada indication and its recommended dosage of 100 mcg or 200 mcg once daily for FF. Trial participants were aged 37 to 47 years on average, the majority were female, and had a history of asthma for more than 10 years. According to the clinical expert consulted on this review, this represents a typical adult patient population for asthma treatment in clinical practice, but may underrepresent pediatric and adolescent patients younger than 18 years. However, the clinical expert had some concerns about baseline severity in terms of per cent predicted FEV_1 and FEV_1 reversibility; the reported values might indicate sub-optimally treated asthma patients. This might increase the bias of comparison with placebo; patients in the active treatment groups would have had their treatment dose optimized, while placebo patients would have had their suboptimal active ICS switched to placebo. The patient populations differed from one study to another in terms of pre-study asthma medication, which ranged from SABAs alone to high doses of ICSs; this might indicate different disease severity in the included studies.

4.2 Interpretation of Results

4.2.1 Efficacy

All included trials documented varying improvements by FF on lung function in the enrolled population, where FEV_1 ranged from 2.1 L to 2.4 L at baseline. The average increase from baseline to end point in patients treated with FF 100 mcg or 200 mcg ranged from 0.16 L to 0.37 L. There is limited evidence indicating that the MCID for FEV_1 is a 10.4% change from baseline; however, the included studies did not provide the corresponding percentage change from baseline, and therefore the clinical significance of treatment could not be concluded. There was a clear time-dependent effect on FEV_1 that showed a decreasing change of FEV_1 volume from the eight-week study to the 24-week studies. No dose-dependent effect on FEV_1 was evident between FF 100 mcg and 200 mcg twice daily. The increases, although numerically small, may be clinically meaningful because patients entered the study using ICSs as maintenance therapy, which was withdrawn and switched to the assigned treatment at baseline. Therefore, the increases at least suggest continued maintenance of the previous ICS treatment effect. However, interpretation of the change in FEV_1 from baseline needs to take into account that oral corticosteroids and bronchodilators, including LABAs and anticholinergics, were withdrawn upon entry into the treatment period. It is therefore possible that in real-world practice, where FF is likely to be used with these standard therapies for the control of moderate or severe asthma, the beneficial effect of FF may be attenuated compared with the effect observed in the trials. FF 100 mcg and 200 mcg were associated with statistically significantly larger change from baseline to end point in FEV_1 than placebo (the LS mean difference ranged from 0.136 L to 0.23 L). Compared with FP, FF 200 mcg once daily was associated with non-inferior change in FEV_1 at a non-inferiority margin of –0.125 L; the mean difference was 0.018 L (95% CI: to –0.066 to 0.102). Non-inferiority was confirmed in both the ITT and PP analyses.

Evaluation of PEF showed a change from baseline that ranged from –0.4 L/min (deterioration at 12 weeks) to 16 L/min (amelioration at eight weeks). FF effect on PEF followed a trend similar to that seen with FEV_1 outcome — a larger change from baseline at eight weeks (30 L/min to 36 L/min) that reached as low as 14 L/min at 24 weeks. The dose effect was also not evident. When FF was compared with

placebo, it showed a statistically significant difference in change from baseline in PEF in the eight-week and 12-week studies, and the LS mean difference (*P* value) ranged from 16 L/min to 22 L/min. However, the difference versus placebo was not statistically significant within the 24-week study. These results, along with FEV_1 findings, raise some concerns about the comparative efficacy of FF versus placebo on longer treatment durations. Comparison of FF versus FP was not reported in the included studies. When FF was compared with the combination of FF/VI, it was shown that the combination therapy was associated with better PEF results (larger change in PEF); the differences (*P* values) were 12 L/min (0.001) and 31 L/min (< 0.001), respectively.

Asthma symptoms are recognized as important outcomes of the disease. The incidence of severe asthma exacerbation was low in general, ranging from 0% to 4% except in one study. During Study FFA-496, almost 13% of the included patients reported severe asthma during the 24 weeks of treatment. The higher rate of exacerbations in this study could not be explained. When the active treatments were considered, the results for asthma symptom-free, 24-hour periods showed a decreasing trend in percentage of symptom-free periods from the shortest study to the longest ones; the change from baseline varied from 17% to 19% in the eight-week study, and from 32% to 38% in the 24-week studies. There was no clear association between asthma symptom-free 24-hour periods and a particular active treatment, but the association could be inferred for the treatment duration. Placebo group showed a steady improvement from baseline in terms of symptom-free periods that ranged from 11.3% to 18.0%. When FF was compared with placebo, results showed a statistically significantly larger improvement with FF than placebo in two studies (one at eight weeks and one at 24 weeks); in the third placebo study, however, the difference was not statistically significant at 12 weeks.

Quality-of-life measures can provide a complete picture of the improvement in key patient-identified outcomes such as pulmonary function and exacerbations. Results of AQLQ + 12 showed that all treatment groups, including placebo, achieved a mean change from baseline score of more than 0.5 (the approximate MCID threshold proposed by the clinical expert). The comparative results of FF 100 mcg versus placebo was not consistent; it showed a statistically significant difference in one study (FFA-059) (mean difference 0.33; *P* = 0.007), and a non-statistically significant difference in another study (HZA-827) (mean difference 0.15; *P* = 0.073).

4.2.2 Harms

The overall incidence of AEs in patients taking FF was comparable to FP, but both FF and FP were associated with a higher incidence of AEs than placebo. According to the clinical expert, placebo groups were expected to present with more frequent AEs related to the progression of asthma without ICS treatment. However, no clear explanation could be provided for the discrepancy between the expected and reported and AE rates. SAEs were relatively rare (0% to 3%); they did not present any evident association with the treatment groups. No deaths were reported in any of the included studies. The most common AEs reported in any treatment arm and across all studies included bronchitis, headache, nasopharyngitis, and upper respiratory tract infection. Infections and infestations were reported more often in the FF 100 mcg group compared with the FP groups, but the difference was not evident when FF 200 mcg was considered.

The manufacturer provided data from three long-term studies for FF either alone or in combination with VI.[27] A total of 303 patients were treated for a duration of 48 to 52 weeks, and 537 patients were treated for more than 52 weeks. In order to determine whether there were differences in the AE profile as time on treatment increased, and to identify the occurrence of new AEs that could be associated with increased exposure to the study drug, the profile for AEs with an onset ≤ 6 months was compared with

the profile of AEs with an onset of > 6 months in the two long-term studies (HZA106837 and HZA113989).[5,40] Overall, there did not appear to be differences in the AE profile of FF 100 as time on treatment increased. There was no pattern of occurrence that would suggest a difference in the AE profile with shorter or longer exposure to study medication.

4.3 Potential Place in Therapy[1]

The gold standard in treatment of stable asthma is ICSs or the combination of ICS and LABAs (ICS/LABA). Currently, five ICSs are approved in Canada: beclomethasone, budesonide, ciclesonide, FP, and mometasone. Their place in therapy is determined by the differences in the devices used to deliver the medication, the "potency" of the corticosteroids, and the ability to adjust the dose (the range of accepted dosage for each inhaler varies).

Multiple limitations exist in establishing the place in therapy for FF. First, the equivalence in potency, as compared with other ICSs, is not available for FF. Second, related to the dosing, ciclesonide offers a wide range of dosing, allowing titration and adjustment of the dose to changing symptoms (during, for example, a viral episode or during allergy season) without needing a new treatment. This does not seem possible with FF, based on the studies completed to date. Third, understanding the ease of use of the device is critical, as poorly administered medication is counterproductive.[41] Some studies are available (e.g., Ellipta versus Breezhaler),[42] but little evidence exists to compare devices used to deliver ICSs (i.e., metered-dose inhalers and diskuses), although it seems that the Ellipta device may have the potential to minimize inhaler-related handling errors and improve adherence.[43] Fourth, the side-effect profile is an important consideration, as described elsewhere in the review).

In conclusion, it is somewhat difficult to assess the place in treatment of FF with the information currently available. It does provide a new device that may be easier to use than the current devices available for certain patients, but the difficulty in comparing the ICS dose and the lack of flexibility in dosing (100 mcg or 200 mcg with no possibility of increasing the dose in case of worsening of symptoms) limits its use compared with some ICSs currently available.

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

5. CONCLUSIONS

Five RCTs were included in which FF 100 mcg and 200 mcg were studied for eight weeks to 24 weeks in patients aged 12 years and older with steroid-responsive bronchial asthma. Other groups in these RCTs were treated with FP (100 mcg, 250 mcg, or 500 mcg twice daily), combination FF/VI (100 mcg/25 mcg or 200 mcg/25 mcg daily), or placebo. The results suggest that, compared with placebo, FP 100 mcg and 200 mcg both improved respiratory measures (FEV and PEF), reduced the incidence of asthma exacerbations, and increased the number of days without asthma symptoms though 24 weeks. However, FF does not appear to consistently improve quality of life.

No statistically significant differences between the FF 100 mcg and 200 mcg doses were reported in the included studies. Only limited conclusions regarding the comparative efficacy between FF and FP can be made, as no formal statistical analyses comparing FF and FP were made in the included studies other than in one non-inferiority trial. Trials were inadequately powered to assess outcomes identified as important by patients and were of insufficient duration to assess long-term outcomes with a medication routinely used in chronic asthma. However, FF appears to have similar efficacy compared with equivalent doses of FP. FF is less effective than combination FF/VI. Whether this conclusion applies for exposure periods that exceed 24 weeks is unknown. FF and FP appear to have similar harms profiles, although longer-term studies are needed to elucidate the harms of FF beyond 24 weeks of exposure.

APPENDIX 1: PATIENT INPUT SUMMARY

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

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

One patient group submitted input.

The Asthma Society of Canada/National Asthma Patient Alliance is a national charitable volunteer-supported organization committed to enhancing the quality of life and health for people living with asthma and associated allergies. The Asthma Society provides health education services, advocates on behalf of Canadians with asthma, and engages in research to improve asthma prevention and management strategies. The Asthma Society receives approximately 20% of its funding from pharmaceutical companies, including GlaxoSmithKline, through unrestricted grants, consulting fees, or other fee-for-service contracts. The Asthma Society made no statement with regard to possible conflicts of interest in the preparation of this submission.

2. Condition and Current Therapy-Related Information

Information for this submission was attained through an online survey sent to members of the National Asthma Patient Alliance across Canada in June 2015. A total of 110 responses were received; 92% were persons with asthma and 7% were caregivers.

Most patients (82%) with asthma indicated that asthma restricts their physical activity and time outdoors, and 35% mentioned that missed days of work or school due to asthma had a significant impact. Others noted the negative stigma of asthma (31%) and the impact asthma had on their family or caregivers (24%). Asthma affected sleep (51%) and social activities (34%) for many patients and caregivers. Others indicated that asthma affected their job opportunities, personal relationships, and ability to do household chores. The most important aspects of asthma to control were day-to-day symptoms (48%) and exacerbations (39%). Others felt medication costs and dosage frequency were important.

Most patients surveyed were using a reliever medication (e.g., Ventolin, Bricanyl; 78%) or a combination medication such as Advair or Symbicort (74%), and 43% were using an inhaled corticosteroid to manage their asthma. Other medications used included leukotriene receptor antagonists, oral corticosteroids, long-acting beta2-agonists (LABAs), and anti-immunoglobulin E (anti-IgE) biologics. Patients indicated that current treatment can be inconvenient and can often result in missed doses and reduced medication compliance. Sixty-nine per cent of patients felt their treatment was effective or very effective; however, a significant proportion felt their treatment was only somewhat effective (29%) or not very effective (3%). Side effects such as weight gain, hoarseness, dry throat, increased heart rate, difficulty sleeping, headaches, mood or behaviour changes and thrush were difficult to tolerate. Costs of treatments were a major barrier when trying to find an ideal treatment.

Caregivers worry that their loved one will suffer an exacerbation or an asthma attack. Missed days of work and school were a challenge, as was the potential for hospital visits and admissions, and the frequent doctors' visits. Costs of medication, the need to manage multiple medications, and doses per day were also a concern to caregivers.

3. Related Information About the Drug Being Reviewed

Having had no experience with the drug under review, 62% of patients felt that a new once-daily medication would improve their lives. A similar proportion of patients felt they would be more likely to take their medication regularly if they only had to take it once daily.

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:	July 26, 2015
Alerts:	Biweekly search updates until November 18, 2015
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
*	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**	**Results**
1	(Arnuity Ellipta* or Alisade* or Allermist* or Avamys* or FF* or furamist* or Veramyst* or flovent diskus or flovent HFA or GSK 685 698* or GSK 685698* or GW 685698* or GW685698* or UNII-JS86977WNV or UNIIJS86977WNV).ti,ab,sh,hw,ot.	816
2	((arnuity or (fluticasone adj2 furoate) or flovent or Allegro or Flixotide) adj3 (ellipta* or oral* or inhal*)).ti,ab,sh,hw,ot.	119
3	(397864-44-7 or "397864447" or JS86977WNV).rn,nm.	499
4	1 or 2 or 3	860
5	4 use pmez	204
6	*FF/	187
7	(Arnuity Ellipta* or Alisade* or Allermist* or Avamys* or FF* or furamist* or Veramyst* or GSK 685 698* or GSK 685698* or GW 685698* or GW685698* or UNII-JS86977WNV or UNIIJS86977WNV).ti,ab.	478
8	((arnuity or (fluticasone adj2 furoate) or flovent or Allegro or Flixotide) adj3 (ellipta* or oral* or inhal*)).ti,ab.	117
9	6 or 7 or 8	532
10	conference abstract.pt.	1925569
11	9 not 10	412
12	11 use oemezd	219
13	5 or 12	423
14	remove duplicates from 13	253

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:	July 2015
Limited Update:	November 2015
Keywords:	Arnuity Ellipta, Fluticasone Furoate, 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
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials
- Canadian Drug Formularies
- Databases (free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Bleecker ER et al. 2012[44]	Non-pivotal phase 2
Busse WW et al. 2012[45]	
Medley H et al. 2012[46]	
Woodcock A et al. 2011[47]	
Woodcock A et al. 2011[48]	
Bodzenta-Lukaszky A et al. 2013[49]	Not an intervention of interest
Busse WW et al. 2013[50]	
Busse WW et al. 2014[51]	
Woodcock A et al. 2013[52]	
Woodcock A et al. 2015[53]	
Batman ED et al. 2014[54]	
Lin J et al. 2015[55]	Not a population/intervention of interest

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 12: RESULTS OF ACUTE EXACERBATIONS OF ASTHMA

	FFA-687 (8 weeks)				HZA-827 (12 weeks)			HZA-829 (24 weeks)			FFA-059 (24 weeks)			FFA-496 (24 weeks)	
Drug/Dosage (mcg)	**FF 100**	**FF 200**	**FP 100**	**PBO**	**FF 100**	**FF/VI 100/25**	**PBO**	**FF 200**	**FF/VI 200/25**	**FP 500**	**FF 100**	**FP 250**	**PBO**	**FF 100**	**FF 200**
Total, N	**110**	**95**	**102**	**94**	**205**	**201**	**203**	**194**	**197**	**195**	**114**	**114**	**115**	**108**	**111**
Severe asthma exacerbations,[a] n (%)	3 (3)	1 (1)	2 (2)	0	4 (2)	1 (< 1)	9 (4)	6 (3)	0	2 (1)	2 (2)	2 (2)	4 (3)	14 (13)	13 (12)
FF vs. PBO	NR				NR			NR			NR			NR	
FF vs. FP															

FF = fluticasone furoate (100 mcg or 200 mcg once daily); FP = fluticasone propionate (100 mcg, 250 mcg, or 500 mcg twice daily); NR = not reported; PBO = placebo; VI = vilanterol; vs = versus (25 mcg once daily).

[a] Acute exacerbations were not explicitly reported; however, the manufacturer reported unscheduled physician visits due to severe exacerbation as part of other outcomes (unscheduled health care contacts/resource utilization or adverse events).

Source: Clinical Study Reports.[1-6]

TABLE 13: RESULTS OF ASTHMA SYMPTOM-FREE 24-HOUR PERIODS

	FFA-687 (8 weeks)				HZA-827 (12 weeks)			HZA-829 (24 weeks)			FFA-059 (24 weeks)			FFA-496 (24 weeks)	
Drug/Dosage (mcg)	**FF 100**	**FF 200**	**FP 100**	**PBO**	**FF 100**	**FF/VI 100/25**	**PBO**	**FF 200**	**FF/VI 200/25**	**FP 500**	**FF 100**	**FP 250**	**PBO**	**FF 100**	**FF 200**
Total, N	**110**	**95**	**102**	**94**	**205**	**201**	**203**	**194**	**197**	**195**	**114**	**114**	**115**	**108**	**111**
% of symptom-free 24-hour periods															
Baseline, mean (SD)	14.2 (21.6)	8.3 (17.0)	9.2 (18.9)	13.5 (22.6)	5.8 (16.5)	5.0 (15.2)	3.5 (12.8)	4.7 (16.1)	5.1 (15.2)	2.7 (9.8)	7.9 (20.5)	7.0 (21.0)	3.9 (10.6)	6.1 (17.7)	4.9 (14.3)
From week 1 to the end of DB period, mean (SD)	51.8 (35.0)	40.7 (36.6)	43.3 (35.7)	31.5 (34.9)	25.2 (32.6)	37.5 (36.3)	19.1 (28.7)	25.8 (33.9)	34.4 (37.9)	26.9 (33.7)	26.5 (33.7)	26.0 (34.6)	15.2 (26.4)	22.7 (30.7)	25.4 (31.9)
Change from baseline, mean (SD)	37.6 (33.0)	32.3 (34.4)	34.1 (34.1)	18.0 (28.5)	19.5 (30.0)	32.5 (36.4)	15.6 (29.9)	21.1 (31.4)	29.4 (34.9)	24.4 (32.3)	18.6 (30.9)	19.0 (33.1)	11.3 (26.7)	16.6 (30.6)	20.4 (29.4)
LS mean change,[a] (SE)	38.7 (3.0)	31.7 (3.2)	33.3 (3.1)	18.4 (3.2)	20.4 (2.1)	32.5 (2.1)	14.6 (2.2)	21.0 (2.32)	29.3 (2.29)	24.5 (2.31)	19.3 (2.8)	19.2 (2.8)	10.4 (2.8)	17.5 (2.80)	19.6 (2.79)
LS mean difference vs. PBO; *P* value	20.2; < 0.001	13.2; 0.004	14.9; < 0.001	NA	5.8[b]; **0.055**	18.0; < 0.001	NA	NA	NA	NA	8.9[b] 0.025	8.8 0.025	NA		
LS mean difference FF vs. FP or FF/VI[c] (95% CI), *P* value	NR	NA	NA	NA	NA	–12.1; 0.001	NA	NA	–8.4; 0.01	NR	NR	NA	NA	–2.1 (–9.9 to 5.7)	

CI = confidence interval; DB = double-blind; FF = fluticasone furoate (100 mcg or 200 mcg once daily); FP = fluticasone propionate (100 mcg, 250 mcg, or 500 mcg twice daily); LS = least squares; NA = not applicable; NR = not reported; PBO = placebo; SD = standard deviation; SE = standard error; VI = vilanterol (25 mcg); vs = versus.

[a] ANCOVA model with effects due to baseline percentage, region, sex, age, and treatment group.

[b] This outcome is number 5 on the hierarchical testing; statistical significance is concluded only if statistical significance is established for trough FEV_1, rescue-free 24-hour periods, evening and morning PEF.

[c] LS mean differences = FF (lowest dose in the study) – other groups.

Source: Clinical Study Reports.[1-4,6]

TABLE 14: RESULTS OF EVENING TROUGH FEV_1 (ITT/LOCF) ABSOLUTE VOLUME

	FFA-687 (8 weeks)				HZA-827 (12 weeks)			HZA-829 (24 weeks)			FFA-059 (24 weeks)			FFA-496 (24 weeks)	
Drug/Dosage (mcg)	**FF 100**	**FF 200**	**FP 100**	**PBO**	**FF 100**	**FF/VI 100/25**	**PBO**	**FF 200**	**FF/VI 200/25**	**FP 500**	**FF 100**	**FP 250**	**PBO**	**FF 100**	**FF 200**
Total, N	**110**	**95**	**102**	**94**	**205**	**201**	**203**	**194**	**197**	**195**	**114**	**114**	**115**	**108**	**111**
Baseline (L), mean (SD)	2.42 (0.67)	2.21 (0.65)	2.34 (0.72)	2.37 (0.68)	2.29 (0.62)	2.34 (0.64)	2.33 (0.63)	2.19 (0.68)	2.13 (0.65)	2.14 (0.67)	2.37 (0.63)	2.36 (0.73)	2.33 (0.65)	NR	NR
End of DB period (L), mean (SD)	2.78 (0.82)	2.58 (0.84)	2.58 (0.86)	2.52 (0.82)	NR			2.43 (0.86)	2.54 (0.86)	2.31 (0.77)	2.53 (0.73)	2.52 (0.84)	2.35 (0.80)	2.24 (0.74)	2.38 (0.80)
Change from baseline, mean (SD)	0.36 (0.49)	0.36 (0.52)	0.24 (0.40)	0.14 (0.46)	NR			0.22 (0.50)	0.39 (0.47)	0.17 (0.39)	0.17 (0.45)	0.15 (0.40)	0.02 (0.47)	0.20 (0.41)	0.29 (0.48)
LS mean change[a], (SE)	0.34 (0.04)	0.37 (0.04)	0.24 (0.04)	0.14 (0.04)	0.33 (0.03)	0.37 (0.03)	0.20 (0.03)	0.20 (0.03)	0.39 (0.03)	0.18 (0.03)	0.16 (0.04)	0.16 (0.04)	0.02 (0.04)	0.21 (0.04)	0.28 (0.04)
Difference[b] vs. PBO; *P* value	0.20; < 0.001	0.23; < 0.001	0.11; 0.074	NA	0.136; 0.002	0.172; 0.001	NA	NA	NA	NA	0.15; 0.009	0.15; 0.011	NA	NR	
Difference[b] vs. active groups (95% CI); *P* value	NR	NR	NA	NA	–0.04; 0.405	NA	NA	NA	–0.19; < 0.001	+0.018; > 0.05[c]	NR	NA		–0.077 (–04220.192 to 0.039)	

CI = confidence interval; DB = double-blind; FF = fluticasone furoate (100 mcg or 200 mcg once daily); FP = fluticasone propionate (100 mcg, 250 mcg, or 500 mcg twice daily); ITT = intention-to-treat; LOCF = last observation carried forward; LS = least squares; NA = not applicable; NR = not reported; PBO = placebo; SD = standard deviation; SE = standard error; VI = vilanterol; vs = versus (25 mcg).

[a] ANCOVA model with effects due to baseline value, region, sex, and treatment group.

[b] LS mean differences = FF (lowest dose in the study) – other groups.

[c] ITT results CI ranged from to –0.066 L to 0.102 L; non-inferiority margin was pre-defined as –0.125 L. Per-protocol results showed a difference of 0.043 L (–0.048 to 0.133).

Source: Clinical Study Reports.[1-6]

TABLE 15: RESULTS OF WEIGHTED MEAN (0 TO 24 HOURS) FEV_1 (ITT/LOCF)

	HZA-827 (12 weeks)			HZA-829 (24 weeks)		
Drug/Dosage (mcg)	**FF 100**	**FF/VI 100/25**	**PBO**	**FF 200**	**FF/VI 200/25**	**FP 500**
Total, N	**205**	**201**	**203**	**194**	**197**	**195**
Baseline (L), mean (SD)	NR			NR		
End of DB period (L), mean (SD)	2.66 (0.78)	2.86 (0.82)	2.60 (0.87)	2.66 (0.85)	2.72 (0.95)	2.32 (0.79)
Change from baseline, mean (SD)	0.38 (0.50)	0.51 (0.52)	0.25 (0.48)	0.35 (0.47)	0.47 (0.58)	0.23 (0.46)
LS mean change[a], (SE)	0.40 (0.043)	0.51 (0.043)	0.21 (0.046)	0.33 (0.046)	0.46 (0.047)	0.26 (0.048)
Difference vs. PBO[b]; *P* value	0.186; 0.003	0.302; < 0.001	NA	NA		
Difference[b] vs. active treatments (95% CI), *P* value	NA	–0.116; 0.060	NA	NA	–0.14; 0.048	NR

ANCOVA = analysis of covariance; CI = confidence interval; DB = double-blind; FF = fluticasone furoate (100 mcg or 200 mcg once daily); FP = fluticasone propionate (100, 250 mcg, or 500 mcg twice daily); ITT = intention-to-treat; LOCF = last observation carried forward; LS = least squares; NA = not applicable; NR = not reported; PBO= placebo; SD = standard deviation; SE = standard error; VI = vilanterol; vs = versus (25 mcg).

[a] ANCOVA model with effects due to baseline value, region, sex, and treatment group.

[b] LS mean differences = FF (lowest dose in the study) – other groups.

Source: Clinical Study Reports.[3,4,6]

TABLE 16: RESULTS OF EVENING PEAK EXPIRATORY FLOW (ITT/LOCF)

	FFA-687 (8 weeks)				HZA-827 (12 weeks)			HZA-829 (24 weeks)			FFA-059 (24 weeks)			FFA-496 (24 weeks)	
Drug/Dosage (mcg)	**FF 100**	**FF 200**	**FP 100**	**PBO**	**FF 100**	**FF/VI 100/25**	**PBO**	**FF 200**	**FF/VI 200/25**	**FP 500**	**FF 100**	**FP 250**	**PBO**	**FF 100**	**FF 200**
Total, N	**110**	**95**	**102**	**94**	**205**	**201**	**203**	**194**	**197**	**195**	**114**	**114**	**115**	**108**	**111**
Baseline (L/min), mean (SD)	372.9 (129)	337.3 (106)	347.2 (125)	355.4 (130)	375.0 (113)	370.2 (123)	367.8 (110)	347.8 (120.1)	342.6 (112.4)	344.3 (116)	369.8 (113)	355.3 (110)	358.7 (115)	340.5 (114)	330.3 (108)
From week 1 to the end of DB period (L/min), mean (SD)	397.7 (124)	369.6 (102)	373.3 (124)	366.7 (123)	388.0 (107)	396.6 (117)	367.6 (106)	357.7 (121)	382.7 (119)	357.7 (113)	370.4 (111)	359.1 (111)	358.2 (110)	345.0 (114)	341.8 (101)
Change from baseline, mean (SD)	24.8 (43.6)	32.3 (52.7)	26.2 (38.0)	11.3 (40.4)	12.9 (37.9)	26.4 (36.2)	–0.6 (32.2)	9.6 (35.0)	40.1 (54.4)	12.8 (39.0)	1.2 (30.7)	4.0 (30.0)	–0.7 (48.4)	4.4 (37.5)	8.7 (37.4)
LS mean change,[a] (SE)	25.7 (3.90)	31.3 (4.20)	24.4 (4.04)	9.6 (4.21)	14.1 (2.34)	26.4 (2.35)	–1.8 (2.36)	9.1 (2.98)	39.8 (2.93)	13.6 (2.96)	1.5 (3.39)	4.3 (3.4)	–1.3 (3.36)	5.9 (3.26)	7.2 (3.25)
Difference[c] vs. PBO; *P* value	16.1; 0.005	21.7; < 0.001	14.9; 0.011	NA	15.9; < 0.001	28.2; < 0.001	NA	NA			2.8[b]; 0.564	5.5; 0.248	NA	NA	
Difference[c] vs. active groups (95% CI), *P* value	NR	NR	NA	NA	NA	–12.3; 0.001	NA	NA	–30.7; < 0.001	NR	NR	NA	NA	–1.3 (–10.4, 7.8)	

ANCOVA = analysis of covariance; CI = confidence interval; FF = fluticasone furoate (100 mcg or 200 mcg once daily); FP = fluticasone propionate (100 mcg, 250 mcg, or 500 mcg twice daily); ITT = intention-to-treat; LOCF = last observation carried forward; LS = least squares; NA = not applicable; NR = not reported; PEF = peak expiratory flow; PBO= placebo; SD = standard deviation; SE = standard error; VI = vilanterol; vs = versus (25 mcg).

[a] ANCOVA model with effects due to baseline value, region, sex, and treatment group.

[b] This outcome is number 3 on the hierarchical testing; statistical insignificance indicates that results for morning PEF, symptom-free 24 hour periods, and AQLQ + 12 are only descriptive and not conclusive.

[c] LS mean differences = FF (lowest dose in the study) – other groups.

Source: Clinical Study Reports.[1-6]

TABLE 17: RESULTS OF MORNING PEAK EXPIRATORY FLOW (ITT/LOCF)

	FFA-687 (8 weeks)				HZA-827 (12 weeks)			HZA-829 (24 weeks)			FFA-059 (24 weeks)			FFA-496 (24 weeks)	
Drug/Dosage (mcg)	**FF 100**	**FF 200**	**FP 100**	**PBO**	**FF 100**	**FF/VI 100/25**	**PBO**	**FF 200**	**FF/VI 200/25**	**FP 500**	**FF 100**	**FP 250**	**PBO**	**FF 100**	**FF 200**
Total, N	**110**	**95**	**102**	**94**	**205**	**201**	**203**	**194**	**197**	**195**	**114**	**114**	**115**	**108**	**111**
Baseline (L/min), mean (SD)	362.2 (125)	326.0 (103)	337.2 (127)	342.7 (128)	366.3 (112)	361.5 (120)	355.5 (112)	332.9 (123.6)	327.4 (113.3)	330.2 (114.1)	350.4 (113)	347.2 (112)	347.3 (112)	329.3 (111.2)	323.1 (111.6)
From week 1 to the end of DB period (L/min), mean (SD)	390.8 (125)	362.5 (102)	364.6 (123)	358.5 (123)	383.0 (108)	394.1 (116)	356.9 (107)	352.1 (120.3)	379.5 (120.4)	348.3 (114.4)	364.4 (110)	356.2 (112)	352.7 (109)	341.3 (114.7)	340.1 (100.9)
Change from baseline, mean (SD)	28.6 (46.5)	36.5 (54.9)	27.4 (41.3)	15.8 (38.4)	16.7 (36.5)	32.6 (41.0)	1.5 (32.8)	18.6 (36.9)	52.1 (52.4)	18.2 (38.7)	14.4 (33.5)	9.0 (31.0)	5.5 (48.7)	12.0 (35.1)	14.6 (38.7)
LS mean change[a], (SE)	29.5 (4.0)	35.6 (4.3)	25.6 (4.1)	13.6 (4.3)	18.3 (2.4)	32.9 (2.4)	–0.4 (2.4)	18.2 (3.0)	51.8 (2.9)	18.8 (3.0)	13.9 (3.5)	9.9 (3.5)	5.0 (3.5)	13.4 (3.22)	13.2 (3.20)
Difference[c] vs. PBO; *P* value	15.9; 0.006	22.0; < 0.001	12.1; 0.41	NA	18.7; < 0.001	33.3; < 0.001	NA				8.9; 0.071	4.9; 0.319	NA		
Difference[c] vs. active groups (95% CI), *P* value	NR	NR	NA	NA	–14.6; 0.001	NA	NA		32.9; < 0.001	NR	NR	NA	NA	0.2 (–8.8, 9.2)	

ANCOVA = analysis of covariance; CI = confidence interval; DB = double-blind; FF = fluticasone furoate (100 mcg or 200 mcg once daily); FP = fluticasone propionate (100 mcg, 250 mcg, or 500 mcg twice daily); ITT = intention-to-treat; LOCF = last observation carried forward; LS = least squares; NA = not applicable; NR = not reported; PEF = peak expiratory flow; PBO = placebo; SD = standard deviation; SE = standard error; VI = vilanterol; vs = versus (25 mcg).

[a] ANCOVA model with effects due to baseline value, region, sex, and treatment group.

[b] LS mean differences =FF (lowest dose in the study) – other groups.

Source: Clinical Study Reports.[1-6]

TABLE 18: RESULTS OF AQLQ +12 TOTAL SCORE

	HZA-827 (12 weeks)			HZA-829 (24 weeks)			FFA-059 (24 weeks)		
Drug/Dosage (mcg)	**FF 100**	**FF/VI 100/25**	**PBO**	**FF 200**	**FF/VI 200/25**	**FP 500**	**FF 100**	**FP 250**	**PBO**
Total, N	**205**	**201**	**203**	**194**	**197**	**195**	**114**	**114**	**115**
Baseline, mean (SD)	4.69 (0.89)	4.78 (1.00)	4.78 (1.03)	4.5 (1.00)	4.37 (0.92)	4.45 (1.05)	4.81 (1.13)	4.76 (1.04)	4.95 (0.97)
At the end of DB period, mean (SD)	5.46 (0.88)	5.69 (0.89)	5.39 (0.85)	5.38 (1.13)	5.35 (1.04)	5.35 (1.09)	5.73 (0.91)	5.53 (1.10)	5.48 (1.01)
Change from baseline, mean (SD)	0.79 (0.91)	0.85 (0.92)	0.64 (0.85)	0.92 (0.87)	0.93 (0.89)	0.85 (1.03)	0.84 (0.89)	0.68 (1.01)	0.51 (0.91)
LS mean change[a], (SE)	0.76 (0.06)	0.91 (0.06)	0.61 (0.06)	0.88 (0.07)	0.93 (0.07)	0.90 (0.07)	0.84 (0.08)	0.67 (0.08)	0.51 (0.09)
Difference vs. PBO[b]; *P* value	0.15; 0.073	0.30; < 0.001	NA	NA			0.33; 0.007	0.16; 0.185	NA
Difference[b] vs. active treatments (95% CI), *P* value	NA	–0.15; 0.059	NA	NA	–0.05; 0.59	NR	NR	NA	NA

ANCOVA = analysis of covariance; AQLQ +12 = Asthma Quality of Life Questionnaire for 12 years and older; CI = confidence interval; DB = double-blind; FF = fluticasone furoate (100 mcg or 200 mcg once daily); FP = fluticasone propionate (100, 250 or 500 mcg twice daily); LS = least squares; NA = not applicable; NR = not reported; PBO = placebo; SD = standard deviation; SE = standard error; VI = vilanterol; vs = versus (25 mcg).

[a] ANCOVA model with effects due to baseline percentage, region, sex, age, and treatment group.

[b] LS mean differences = FF (lowest dose in the study) – other groups.

Source: Clinical Study Reports.[1,3,4,6]

TABLE 19: RESULTS OF AQLQ +12 SCORE_ ACTIVITY LIMITATION

	HZA-827 (12 weeks)			HZA-829 (24 weeks)			FFA-059 (24 weeks)		
Drug/Dosage (mcg)	**FF 100**	**FF/VI 100/25**	**PBO**	**FF 200**	**FF/VI 200/25**	**FP 500**	**FF 100**	**FP 250**	**PBO**
Total, N	**205**	**201**	**203**	**194**	**197**	**195**	**114**	**114**	**115**
Baseline, mean (SD)	4.88 (0.90)	4.99 (1.02)	4.97 (1.02)	4.70 (1.08)	4.57 (0.98)	4.69 (1.12)	5.06 (1.18)	5.02 (1.09)	5.15 (1.12)
At the end of DB period, mean (SD)	5.58 (0.91)	5.76 (0.95)	5.50 (0.82)	5.47 (1.13)	5.41 (1.09)	5.44 (1.11)	5.79 (1.02)	5.65 (1.06)	5.63 (1.08)
Change from baseline, mean (SD)	0.69 (0.87)	0.72 (0.93)	0.58 (0.85)	0.79 (0.80)	0.78 (0.89)	0.73 (0.99)	0.63 (0.91)	0.54 (0.89)	0.47 (0.83)
Difference vs. PBO[b]; *P* value	NR	NR	NA	NA			NR	NR	NA
Difference[b] vs. active treatments (95% CI), *P* value	NR	NA	NA	NR	NR	NR	NR	NA	NA

ANCOVA = analysis of covariance; AQLQ +12 = Asthma Quality of Life Questionnaire for 12 years and older; CI = confidence interval; DB = double-blind; FF = fluticasone furoate (100 mcg or 200 mcg once daily); FP = fluticasone propionate (100 mcg, 250 mcg, or 500 mcg twice daily); LS = least squares; NA = not applicable; NR = not reported; PBO = placebo; SD = standard deviation; VI = vilanterol; vs = versus (25 mcg).

[a] ANCOVA model with effects due to baseline percentage, region, sex, age, and treatment group.

[b] LS mean differences = FF (lowest dose in the study) – other groups.

Source: Clinical Study Reports.[1,3,4,6]

TABLE 20: RESULTS OF AQLQ +12 SCORE_ SYMPTOMS

	HZA-827 (12 weeks)			HZA-829 (24 weeks)			FFA-059 (24 weeks)		
Drug/Dosage (mcg)	**FF 100**	**FF/VI 100/25**	**PBO**	**FF 200**	**FF/VI 200/25**	**FP 500**	**FF 100**	**FP 250**	**PBO**
Total, N	**205**	**201**	**203**	**194**	**197**	**195**	**114**	**114**	**115**
Baseline, mean (SD)	4.53 (0.94)	4.64 (1.07)	4.59 (1.06)	4.34 (1.00)	4.22 (0.94)	4.28 (1.06)	4.70 (1.16)	4.58 (1.10)	4.79 (0.97)
At the end of DB period, mean (SD)	5.42 (0.90)	5.66 (0.97)	5.33 (0.92)	5.39 (1.16)	5.39 (1.06)	5.33 (1.13)	5.79 (0.91)	5.54 (1.14)	5.41 (0.98)
Change from baseline, mean (SD)	0.90 (1.02)	0.98 (1.02)	0.74 (0.98)	1.11 (1.02)	1.10 (1.01)	0.99 (1.19)	1.01 (0.96)	0.87 (1.20)	0.61 (1.10)
Difference vs. PBO[b]; *P* value	NR	NR	NA	NA			NR	NR	NA
Difference[b] vs. active treatments (95% CI), *P* value	NR	NA	NA	NR	NR	NR	NR	NA	NA

ANCOVA = analysis of covariance; AQLQ +12 = Asthma Quality of Life Questionnaire for 12 years and older; CI = confidence interval; DB = double-blind; FF = fluticasone furoate (100 mcg or 200 mcg once daily); FP = fluticasone propionate (100, 250 or 500 mcg twice daily); LS = least squares; NA = not applicable; NR = not reported; PBO = placebo; SD = standard deviation; VI = vilanterol; vs = versus (25 mcg).

[a] ANCOVA model with effects due to baseline percentage, region, sex, age, and treatment group.

[b] LS mean differences = FF (lowest dose in the study) – other groups.

Source: Clinical Study Reports.[1,3,4,6]

TABLE 21: RESULTS OF AQLQ +12 SCORE_ EMOTIONAL FUNCTION

	HZA-827 (12 weeks)			HZA-829 (24 weeks)			FFA-059 (24 weeks)		
Drug/Dosage (mcg)	**FF 100**	**FF/VI 100/25**	**PBO**	**FF 200**	**FF/VI 200/25**	**FP 500**	**FF 100**	**FP 250**	**PBO**
Total, N	**205**	**201**	**203**	**194**	**197**	**195**	**114**	**114**	**115**
Baseline, mean (SD)	4.64 (1.25)	4.71 (1.31)	4.88 (1.36)	4.50 (1.27)	4.44 (1.30)	4.53 (1.34)	4.75 (1.46)	4.82 (1.32)	4.97 (1.22)
At the end of DB period, mean (SD)	5.49 (1.09)	5.68 (1.03)	5.50 (1.08)	5.43 (1.33)	5.41 (1.26)	5.43 (5.60)	5.76 (1.18)	5.68 (1.21)	5.59 (1.08)
Change from baseline, mean (SD)	0.93 (1.13)	0.84 (1.19)	0.60 (1.06)	0.94 (1.13)	0.91 (1.16)	0.84 (1.35)	0.96 (1.26)	0.78 (1.30)	0.54 (0.012)
Difference versus PBO[b]; *P* value	NR	NR	NA	NA			NR	NR	NA
Difference[b] vs. active treatments (95% CI), *P* value	NR	NA	NA	NR	NR	NR	NR	NA	NA

ANCOVA = analysis of covariance; AQLQ +12 = Asthma Quality of Life Questionnaire for 12 years and older; CI = confidence interval; DB = double-blind; FF = fluticasone furoate (100 mcg or 200 mcg once daily); FP = fluticasone propionate (100, 250 or 500 mcg twice daily); LS = least squares; NA = not applicable; NR = not reported; PBO = placebo; SD = standard deviation; VI = vilanterol; vs = versus (25 mcg).

[a] ANCOVA model with effects due to baseline percentage, region, sex, age, and treatment group.

[b] LS mean differences = FF (lowest dose in the study) – other groups.

Source: Clinical Study Reports.[1,3,4,6]

TABLE 22: RESULTS OF AQLQ +12 SCORE_ ENVIRONMENTAL STIMULI

	HZA-827 (12 weeks)			HZA-829 (24 weeks)			FFA-059 (24 weeks)		
Drug/Dosage (mcg)	**FF 100**	**FF/VI 100/25**	**PBO**	**FF 200**	**FF/VI 200/25**	**FP 500**	**FF 100**	**FP 250**	**PBO**
Total, N	**205**	**201**	**203**	**194**	**197**	**195**	**114**	**114**	**115**
Baseline, mean (SD)	4.66 (1.15)	4.68 (1.21)	4.69 (1.31)	4.44 (1.34)	4.19 (1.20)	4.25 (1.35)	4.50 (1.34)	4.52 (1.43)	4.86 (1.23)
At the end of DB period, mean (SD)	5.28 (1.17)	5.50 (1.03)	5.14 (1.11)	5.08 (1.45)	5.01 (1.33)	5.04 (1.35)	5.17 (1.31)	5.16 (1.44)	5.10 (1.21)
Change from baseline, mean (SD)	0.67 (1.01)	0.77 (1.21)	0.54 (1.08)	0.66 (1.10)	0.77 (1.12)	0.81 (1.14)	5.42 (1.24)	5.10 (1.49)	5.12 (1.37)
Difference versus PBO[b]; *P* value	NR	NR	NA	NA			NR	NR	NA
Difference[b] vs. active treatments (95% CI), *P* value	NR	NA	NA	NR	NR	NR	NR	NA	NA

ANCOVA = analysis of covariance; AQLQ +12 = Asthma Quality of Life Questionnaire for 12 years and older; CI = confidence interval; DB = double-blind; FF = fluticasone furoate (100 mcg or 200 mcg once daily); FP = fluticasone propionate (100, 250 or 500 mcg twice daily); LS = least squares; NA = not applicable; NR = not reported; PBO= placebo; SD = standard deviation; VI = vilanterol; vs = versus (25 mcg).

[a] ANCOVA model with effects due to baseline percentage, region, sex, age, and treatment group.

[b] LS mean differences = FF (lowest dose in the study) – other groups.

Source: Clinical Study Reports.[1,3,4,6]

TABLE 23: RESULTS OF PERCENTAGE OF RESCUE-FREE 24-HOUR PERIODS

	FFA-687 (8 weeks)				HZA-827 (12 weeks)			HZA-829 (24 weeks)			FFA-059 (24 weeks)			FFA-496 (24 weeks)	
Drug/Dosage (mcg)	**FF 100**	**FF 200**	**FP 100**	**PBO**	**FF 100**	**FF/VI 100/25**	**PBO**	**FF 200**	**FF/VI 200/25**	**FP 500**	**FF 100**	**FP 250**	**PBO**	**FF 100**	**FF 200**
Total, N	**110**	**95**	**102**	**94**	**205**	**201**	**203**	**194**	**197**	**195**	**114**	**113**	**115**	**108**	**111**
Baseline (%), mean (SD)	15.4 (22.3)	9.0 (18.1)	9.8 (19.3)	10.5 (17.7)	15.3 (29.2)	13.4 (27.4)	14.5 (29.9)	7.8 (20.7)	7.6 (19.2)	6.3 (18.0)	13.3 (24.5)	17.1 (30.5)	18.5 (29.2)	14.3 (28.9)	11.5 (25.5)
From week 1 to the end of DB period (%), mean (SD)	54.8 (35.4)	41.5 (36.9)	45.9 (37.0)	33.0 (36.9)	40.9 (37.9)	50.9 (37.8)	32.8 (36.9)	34.4 (37.4)	45.9 (39.1)	37.9 (36.6)	36.0 (37.3)	41.0 (36.9)	24.1 (33.0)	34.6 (36.0)	35.8 (35.3)
Change from baseline, mean (SD)	39.4 (33.9)	32.5 (35.7)	36.1 (35.2)	22.6 (32.3)	25.5 (33.1)	37.5 (37.6)	18.3 (34.5)	26.6 (34.4)	38.3 (36.4)	31.8 (35.2)	22.4 (32.4)	23.9 (35.4)	5.8 (28.4)	20.3 (35.5)	24.1 (31.6)
LS mean change[a], (SE)	40.8 (3.08)	32.0 (3.31)	35.5 (3.18)	21.9 (3.32)	26.5 (2.25)	37.1 (2.26)	17.8 (2.26)	26.6 (2.45)	38.2 (2.42)	31.9 (2.45)	21.3 (2.85)	24.3 (2.83)	6.5 (2.82)	21.3 (3.05)	23.1 (3.03)
Difference[b] vs. PBO; *P* value	18.9; < 0.001	10.1; 0.031	13.7; 0.003	NA	8.7; 0.007	19.3; < 0.001	NA	NA			14.8; < 0.001	17.9; < 0.001	NA	NA	
Difference[b] vs. active treatments (95% CI), *P* value	NR	NR	NA	NA	NA	–10.6; < 0.001	NA	NA	–11.7; < 0.001	NR	NR	NA	NA	–1.8 (–10.3, 6.7)	

ANCOVA = analysis of covariance; CI = confidence interval; DB = double-blind; FF = fluticasone furoate (100 mcg or 200 mcg once daily); FP = fluticasone propionate (100, 250 or 500 mcg twice daily); LS = least squares; NA = not applicable; NR = not reported; PBO = placebo; SD = standard deviation; SE = standard error; VI = vilanterol (25 mcg); vs = versus.

[a] ANCOVA model with effects due to baseline percentage, region, sex, age, and treatment group.

[b] Differences = FF (lowest dose in the study) – other groups.

Source: Clinical Study Reports.[1-6]

TABLE 24: RESULTS OF UNSCHEDULED ASTHMA HEALTH CARE CONTACTS/RESOURCE UTILIZATION

	HZA-827 (12 weeks)			HZA-829 (24 weeks)			FFA-059 (24 weeks)			FFA-496 (24 weeks)	
Drug/Dosage (mcg)	**FF 100**	**FF/VI 100/25**	**PBO**	**FF 200**	**FF/VI 200/25**	**FP 500**	**FF 100**	**FP 250**	**PBO**	**FF 100**	**FF 200**
Total, N	**205**	**201**	**203**	**194**	**197**	**195**	**114**	**114**	**115**	**108**	**111**
All unscheduled visits, mean (SD)	0	0	0	0 (0.07)	0	0	0	0	0	0 (0.1)	0 (0.09)

CSR = Clinical Study Reports; FF = fluticasone furoate (100 mcg or 200 mcg once daily); FP = fluticasone propionate (100, 250 or 500 mcg twice daily); NA = not applicable; NR = not reported; PBO= placebo; SD = standard deviation; VI = vilanterol (25 mcg).
Source: Clinical Study Reports.[1-6]

TABLE 25: PATIENTS WHO USED INHALER CORRECTLY

	HZA-827 (12 weeks)			FFA-496 (24 weeks)	
Drug/Dosage (mcg)	**FF 100**	**FF/VI 100/25**	**PBO**	**FF 100**	**FF 200**
Total, N	**205**	**201**	**203**	**108**	**111**
Did patient use inhaler correctly at baseline?					
Yes, n (%)	196 (96)	188 (94)	194 (96)	102 (95)	104 (94)
No, n (%)	9 (4)	13 (6)	9 (4)	5 (5)	7 (6)
Did patient use inhaler correctly at subsequent visits?					
Yes, n (%)	205 (100)	201 (100)	203 (100)	103 (98)	107 (> 99)
No, n (%)	0	0	0	2 (2)	1 (< 1)

ANCOVA = analysis of covariance; FF = fluticasone furoate (100 mcg or 200 mcg once daily); FP = fluticasone propionate (100, 250 or 500 mcg twice daily); PBO = placebo; VI = vilanterol (25 mcg).
[a] ANCOVA model with effects due to baseline percentage, region, sex, age, and treatment group.
Source: Clinical Study Reports.[1-6]

APPENDIX 5: 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 Quality of Life Questionnaire for patients 12 years and older (AQLQ +12).

Findings

The above outcome measures are briefly summarized in Table 26.

TABLE 26: VALIDITY AND MINIMAL CLINICALLY IMPORTANT DIFFERENCE OF OUTCOME MEASURES

Instrument	Type	Evidence of Validity	MCID	References
FEV_1	FEV_1 is the volume of air that can be forcibly expired in one second after a full inspiration.	Yes	Unknown	None
PEF	PEF is the maximum flow rate achieved during a maximal forceful exhalation, and starting from full lung inflation.	Yes	Unknown	None
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 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

ACQ = Asthma Control Questionnaire; AQLQ +12 = Asthma Quality of Life Questionnaire for 12 years and older; FEV_1 = forced expiratory volume in one second; MCID = minimal clinically important difference; PEF = peak expiratory flow.

FEV_1

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 per cent predicted FEV_1 is one of the commonly reported pulmonary function tests.[29] Considered an acceptable primary end point (although recommended as a secondary clinical end point)

by Health Canada,[30] 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 an inhaled short-acting beta2-agonist (SABA), FEV_1 is used to classify the severity of asthma.[56,57] There seems to be uncertainty, however, regarding the extent to which FEV_1 values are associated with quality of life, as researchers have reported variable correlations — ranging from none to strong[58-61] — among adult and children with asthma. However, FEV_1 values appear to correlate well with important clinical outcomes, including the likelihood of hospitalization.[62] 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.[63]

There appears to be limited evidence of an MCID for FEV_1 among individuals with asthma. In one study of 281 adult asthmatic patients, 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.[64]

PEF

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."[31] 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.[32-34] Alternatively, PEF may be measured using electronic peak flow meters, 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.[65]

There appears to be uncertainty around the extent to which diurnal (daily) variability in PEF measurements are important in diagnosing asthma among adults. For instance, in one study of 123 individuals, of whom 60 had asthma, researchers found PEF variability performed moderately as a diagnostic tool (sensitivity = 64.7%, specificity = 81.8%, positive predictive value = 84.6%, negative predictive value = 60%, and accuracy = 71%).[66] This is in contrast to a previous study, in which researchers found PEF to be a poor predictive tool.[67] Diagnostic accuracy seems to be higher among children with asthma.[68,69] Further, PEF values appear to discriminate between patients with reversible and irreversible airflow obstruction.[70] PEF values also appear to be a valid clinical marker of airway responsiveness and asthma severity.[65] In addition, they seem to correlate well with other measures of lung function, including FEV_1,[71] although there appears to be a paucity of evidence directly linking PEF values with impact on quality of life.

Some trialists have used a value of 25 L/min as an MCID for PEF values among patients with asthma.[35,36] No research, however, seems to support 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.[64] 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.[72]

AQLQ +12

The Asthma Quality of Life Questionnaire for 12 years and older (AQLQ +12) is a patient-reported, disease-specific, health-related quality of life measure that is a variant of the standardized version of the Asthma Quality of Life Questionnaire (AQLQ) developed by Juniper et al.[73] 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 altered one question about "work-related limitations" to ask about "work/school-related limitations."[37] 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 seven-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 to the questions in the respective domains. Patients recall their relevant experiences during the previous two weeks.

The AQLQ +12 was originally validated in a secondary analysis of two clinical trials, which included 2,433 patients with asthma.[37] Overall, in the study, the AQLQ +12 showed high internal consistency at baseline; the Cronbach's alpha ranged from 0.95 to 0.97 depending on the age group (12 to 17 years, 18 years and older) and from which of the two studies the data were analyzed. Conversely, however, the cross-sectional (baseline) construct validity 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, nighttime waking, and amount of rescue medication — was variable, with Pearson correlation coefficients indicating 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, strong known-groups validity, and excellent responsiveness.[38] Internal consistency of the overall instrument remained very high (Cronbach's alpha > 0.90).

No study appears to have formally established the MCID for AQLQ +12, although 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.[37-39]

Conclusion

Overall, FEV_1, PEF, and AQLQ +12 appear to be validated outcomes for use in clinical trials of therapies for patients with asthma. No MCID was found for theses outcomes.

REFERENCES

1. Clinical Study Report: FFA112059. A randomised, double-blind, double-dummy, placebo controlled (with rescue medication), multicenter study to evaluate the efficacy and safety of fluticasone furoate inhalation powder in the treatment of persistent asthma in adults and adolescents. [**CONFIDENTIAL** internal manufacturer's report]. Mississauga (ON): GlaxoSmithKline; 2012.
2. Clinical Study Report: FFA10968. A randomized double-blind, double-dummy, placebo-controlled, parallel-group, multicenter, dose ranging study to evaluate the efficacy and safety of GW685698X inhalation powder administered once daily and fluticasone propionate inhalation powder 100 mcg twice daily compared with placebo for 8 weeks in adolescent and adult subjects with persistent asthma symptomatic on non-steroidal, asthma therapy [**CONFIDENTIAL** internal manufacturer's report]. Mississauga (ON): GlaxoSmithKline; 2008.
3. Clinical Study Report: HZA106827. A randomised, double-blind, placebo-controlled (with rescue medication), parallel group multi-centre study of fluticasone furoate/GW642444 inhalation powder and fluticasone furoate inhalation powder alone in the treatment of persistent asthma in adults and adolescents [**CONFIDENTIAL** internal manufacturer's report]. Mississauga (ON): GlaxoSmithKline; 2011.
4. Clinical Study Report: HZA106829. A randomised, double-blind, parallel group, multicentre study of fluticasone furoate/GW642444 inhalation powder, fluticasone furoate inhalation powder alone, and fluticasone propionate alone in the treatment of persistent asthma in adults and adolescents. [**CONFIDENTIAL** internal manufacturer's report]. Mississauga (ON): GlaxoSmithKline; 2011.
5. Clinical Study Report: HZA106837. A long-term, randomized, double-blind, parallel group study of fluticasone furoate/GW642444 inhalation powder once-daily and fluticasone furoate inhalation powder once-daily in subjects with asthma. [**CONFIDENTIAL** internal manufacturer's report]. Mississauga (ON): GlaxoSmithKline; 2011.
6. Clinical Study Report: FFA114496. A randomised, double-blind, multicentre study to evaluate the efficacy and safety of inhaled fluticasone furoate in the treatment of persistent asthma in adults and adolescents currently receiving mid to high strength inhaled corticosteroids. [**CONFIDENTIAL** internal manufacturer's report]. Mississauga (ON): GlaxoSmithKline; 2012.
7. Lougheed MD, Lemiere C, Dell SD, Ducharme FM, Fitzgerald JM, Leigh R, et al. Canadian Thoracic Society Asthma Management Continuum--2010 consensus summary for children six years of age and over, and adults. Can Respir J [Internet]. 2010 Jan [cited 2015 Sep 28];17(1):15-24. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2866209
8. Global strategy for asthma management and prevention: updated 2015 [Internet]. S.l.: Global Initiative for Asthma; 2015. [cited 2015 Sep 11]. Available from: http://www.ginasthma.org/local/uploads/files/GINA_Report_2015_Aug11.pdf
9. Statistics Canada [Internet]. Ottawa: Statistics Canada. 2015 [cited 2015 Sep 11]. Available from: http://www.statcan.gc.ca/start-debut-eng.html
10. The Lung Association [Internet]. Ottawa: Canadian Lung Association. 2015 [cited 2015 Sep 11]. Available from: http://www.lung.ca/
11. To T, Wang C, Guan J, McLimont S, Gershon AS. What is the lifetime risk of physician-diagnosed asthma in Ontario, Canada? Am J Respir Crit Care Med. 2010 Feb 15;181(4):337-43.
12. Gershon AS, Guan J, Wang C, To T. Trends in asthma prevalence and incidence in Ontario, Canada, 1996-2005: a population study. Am J Epidemiol. 2010 Sep 15;172(6):728-36.

13. Heaney LG, Conway E, Kelly C, Johnston BT, English C, Stevenson M, et al. Predictors of therapy resistant asthma: outcome of a systematic evaluation protocol. Thorax [Internet]. 2003 Jul [cited 2015 Sep 28];58(7):561-6. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1746731

14. Robinson DS, Campbell DA, Durham SR, Pfeffer J, Barnes PJ, Chung KF, et al. Systematic assessment of difficult-to-treat asthma. Eur Respir J. 2003 Sep;22(3):478-83.

15. LindenSmith J, Morrison D, Deveau C, Hernandez *P*. Overdiagnosis of asthma in the community. Can Respir J. 2004 Mar;11(2):111-6.

16. Aaron SD, Vandemheen KL, Boulet LP, McIvor RA, Fitzgerald JM, Hernandez *P*, et al. Overdiagnosis of asthma in obese and nonobese adults. CMAJ [Internet]. 2008 Nov 18 [cited 2015 Sep 11];179(11):1121-31. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2582787

17. PrArnuity™ Ellipta® (fluticasone furoate): 100 mcg and 200 mcg fluticasone furoate dry powder for oral inhalation [product monograph]. Mississauga (ON): GlaxoSmithKline Inc; 2015 Sep 18.

18. PrFLOVENT® HFA (fluticasone propionate inhalation aerosol): 50, 125, and 250 mcg/metered dose; PrFLOVENT® DISKUS® (fluticasone propionate powder for inhalation): 50, 100, 250, and 500 mcg/blister - Corticosteroid for Oral Inhalation [product monograph] [Internet]. Mississauga (ON): GlaxoSmithKline Inc; 2014 Jul 29. [cited 2015 Sep 28]. Available from: http://www.gsk.ca/english/docs-pdf/product-monographs/Flovent.pdf

19. PrASMANEX® Twisthaler® (Mometasone Furoate Dry Powder Inhaler 100 mcg/metered inhalation; 200 mcg/metered inhalation; 400 mcg/metered inhalation): Corticosteroid[product monograph] [Internet]. Kirkland (QC): Merck Canada Inc; 2015 Mar 18. [cited 2015 Sep 28]. Available from: http://www.merck.ca/assets/en/pdf/products/ASMANEX_Twisthaler-PM_E.pdf

20. PrPULMICORT® TURBUHALER® (budesonide; Powder for Oral Inhalation; 100 µg, 200 µg, and 400 µg/ metered dose): Glucocorticosteroid[product monograph] [Internet]. Mississauga (ON): AstraZeneca Canada Inc; 2015 Apr 20. [cited 2015 Sep 28]. 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=1285585477812&ssbinary=true

21. PrQVAR™ Inhalation Aerosol (beclomethasone dipropionate) Metered Dose Aerosol; 50 µg and 100 µg: Corticosteroid for Oral Inhalation [product monograph]. Laval (PQ): Valeant Canada LP; 2013 Sep 18.

22. Bateman ED, Bleecker ER, Lotvall J, Woodcock A, Forth R, Medley H, et al. Dose effect of once-daily fluticasone furoate in persistent asthma: a randomized trial. Respir Med. 2012 May;106(5):642-50.

23. O'Byrne PM, Bleecker ER, Bateman ED, Busse WW, Woodcock A, Forth R, et al. Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma. Eur Respir J [Internet]. 2014 Mar [cited 2015 Sep 28];43(3):773-82. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3938760

24. Bleecker ER, Lotvall J, O'Byrne PM, Woodcock A, Busse WW, Kerwin EM, et al. Fluticasone furoate-vilanterol 100-25 mcg compared with fluticasone furoate 100 mcg in asthma: a randomized trial. J Allergy Clin Immunol Pract. 2014 Sep;2(5):553-61.

25. Lotvall J, Bleecker ER, Busse WW, O'Byrne PM, Woodcock A, Kerwin EM, et al. Efficacy and safety of fluticasone furoate 100 mug once-daily in patients with persistent asthma: a 24-week placebo and active-controlled randomised trial. Respir Med. 2014 Jan;108(1):41-9.

26. Woodcock A, Lotvall J, Busse WW, Bateman ED, Stone S, Ellsworth A, et al. Efficacy and safety of fluticasone furoate 100 mug and 200 mug once daily in the treatment of moderate-severe asthma in adults and adolescents: a 24-week randomised study. BMC Pulm Med [Internet]. 2014 [cited 2015 Sep 28];14:113. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4107726

27. CDR submission: Arnuity Ellipta (fluticasone furoate), 100 mcg and 200 mcg dry powder for oral inhalation. Company: GlaxoSmithKline Inc. [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): GlaxoSmithKline Inc.; 2015 Oct 7.

28. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical review(s) [Internet]. In: Arnuity Ellipta (fluticasone forate inhalation powder): GlaxoSmithKline Inc. Application no.: 204671. Approval date: 12/06/2013. Rockville (MD): The Center; 2014 Jul 18 [cited 2015 Oct 28]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205625Orig1s000MedR.pdf.

29. van Dalen C, Harding E, Parkin J, Cheng S, Pearce N, Douwes J. Suitability of forced expiratory volume in 1 second/forced vital capacity vs percentage of predicted forced expiratory volume in 1 second for the classification of asthma severity in adolescents. Arch Pediatr Adolesc Med. 2008 Dec;162(12):1169-74.

30. Draft guidance document - data requirements for safety and effectiveness of subsequent market entry inhaled corticosteroid products for use in the treatment of asthma for industry [Internet]. Ottawa: Health Canada; 2011. [cited 2015 Aug 12]. Available from: http://www.hc-sc.gc.ca/dhp-mps/consultation/drug-medic/draft_inhal_ebauche_corticost-eng.php

31. Quanjer PH, Lebowitz MD, Gregg I, Miller MR, Pedersen OF. Peak expiratory flow: conclusions and recommendations of a Working Party of the European Respiratory Society. Eur Respir J Suppl. 1997 Feb;24:2S-8S.

32. Hyland ME, Kenyon CA, Allen R, Howarth *P*. Diary keeping in asthma: comparison of written and electronic methods. BMJ [Internet]. 1993 Feb 20 [cited 2015 Sep 28];306(6876):487-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1676776

33. Kamps AW, Roorda RJ, Brand PL. Peak flow diaries in childhood asthma are unreliable. Thorax [Internet]. 2001 Mar [cited 2015 Sep 28];56(3):180-2. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1758788

34. Ireland AM, Wiklund I, Hsieh R, Dale *P*, O'Rourke E. An electronic diary is shown to be more reliable than a paper diary: results from a randomized crossover study in patients with persistent asthma. J Asthma. 2012 Nov;49(9):952-60.

35. Boushey HA, Sorkness CA, King TS, Sullivan SD, Fahy JV, Lazarus SC, et al. Daily versus as-needed corticosteroids for mild persistent asthma. N Engl J Med. 2005 Apr 14;352(15):1519-28.

36. Drazen JM, Israel E, Boushey HA, Chinchilli VM, Fahy JV, Fish JE, et al. Comparison of regularly scheduled with as-needed use of albuterol in mild asthma. Asthma Clinical Research Network. N Engl J Med. 1996 Sep 19;335(12):841-7.

37. Juniper EF, Svensson K, Mork AC, Stahl E. Modification of the asthma quality of life questionnaire (standardised) for patients 12 years and older. Health Qual Life Outcomes [Internet]. 2005 [cited 2015 Aug 12];3:58. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1262746/pdf/1477-7525-3-58.pdf

38. Wyrwich KW, Ireland AM, Navaratnam *P*, Nolte H, Gates DF, Jr. Validation of the AQLQ12+ among adolescents and adults with persistent asthma. Qual Life Res. 2011 Aug;20(6):903-12.

39. Wyrwich KW, Khan SA, Navaratnam *P*, Nolte H, Gates DF, Jr. Validation and agreement across four versions of the asthma control questionnaire in patients with persistent asthma. Respir Med. 2011 May;105(5):698-712.

40. Clinical study report: HZA113989. A long-term treatment study of 52 weeks of once-daily treatment of a combination of fluticasone furoate (FF)/GW642444 for inhalation and once-daily treatment of FF for inhalation in Japanese asthma patients [**CONFIDENTIAL** internal manufacturer's report]. Mississauga (ON): GlaxoSmithKline; 2013.

41. Lavorini F, Fontana GA, Usmani OS. New inhaler devices - the good, the bad and the ugly. Respiration. 2014;88(1):3-15.

42. Komase Y, Asako A, Kobayashi A, Sharma R. Ease-of-use preference for the ELLIPTA(R) dry powder inhaler over a commonly used single-dose capsule dry powder inhaler by inhalation device-naive Japanese volunteers aged 40 years or older. Int J Chron Obstruct Pulmon Dis [Internet]. 2014 [cited 2015 Oct 28];9:1365-75. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4267517

43. Svedsater H, Jacques L, Goldfrad C, Bleecker ER. Ease of use of the ELLIPTA dry powder inhaler: data from three randomised controlled trials in patients with asthma. NPJ Prim Care Respir Med [Internet]. 2014 [cited 2015 Oct 28];24:14019. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4373320

44. Bleecker ER, Bateman ED, Busse WW, Woodcock A, Frith L, House KW, et al. Once-daily fluticasone furoate is efficacious in patients with symptomatic asthma on low-dose inhaled corticosteroids. Ann Allergy Asthma Immunol. 2012 Nov;109(5):353-8.

45. Busse WW, Bleecker ER, Bateman ED, Lotvall J, Forth R, Davis AM, et al. Fluticasone furoate demonstrates efficacy in patients with asthma symptomatic on medium doses of inhaled corticosteroid therapy: an 8-week, randomised, placebo-controlled trial. Thorax. 2012 Jan;67(1):35-41.

46. Medley H, Orozco S, Allen A. Efficacy and safety profile of fluticasone furoate administered once daily in the morning or evening: a randomized, double-blind, double-dummy, placebo-controlled trial in adult and adolescent patients with persistent bronchial asthma. Clin Ther. 2012 Aug;34(8):1683-95.

47. Woodcock A, Bleecker ER, Busse WW, Lotvall J, Snowise NG, Frith L, et al. Fluticasone furoate: once-daily evening treatment versus twice-daily treatment in moderate asthma. Respir Res [Internet]. 2011 [cited 2015 Sep 28];12:160. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3282675

48. Woodcock A, Bateman ED, Busse WW, Lotvall J, Snowise NG, Forth R, et al. Efficacy in asthma of once-daily treatment with fluticasone furoate: a randomized, placebo-controlled trial. Respir Res [Internet]. 2011 [cited 2015 Sep 28];12:132. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3217852

49. Bodzenta-Lukaszyk A, van Noord J, Schroder-Babo W, McAulay K, McIver T. Efficacy and safety profile of fluticasone/formoterol combination therapy compared to its individual components administered concurrently in asthma: a randomised controlled trial. Curr Med Res Opin. 2013 May;29(5):579-88.

50. Busse WW, O'Byrne PM, Bleecker ER, Lotvall J, Woodcock A, Andersen L, et al. Safety and tolerability of the novel inhaled corticosteroid fluticasone furoate in combination with the beta2 agonist vilanterol administered once daily for 52 weeks in patients >=12 years old with asthma: a randomised trial. Thorax [Internet]. 2013 Jun [cited 2015 Sep 28];68(6):513-20. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3664377

51. Busse WW, Bateman ED, O'Byrne PM, Lotvall J, Woodcock A, Medley H, et al. Once-daily fluticasone furoate 50 mcg in mild-to-moderate asthma: a 24-week placebo-controlled randomized trial. Allergy [Internet]. 2014 Nov [cited 2015 Sep 28];69(11):1522-30. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4329337

52. Woodcock A, Bleecker ER, Lotvall J, O'Byrne PM, Bateman ED, Medley H, et al. Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: a randomized trial. Chest [Internet]. 2013 Oct [cited 2015 Jul 29];144(4):1222-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3787916/pdf/chest_144_4_1222.pdf

53. Woodcock AA, Bagdonas A, Boonsawat W, Gibbs MR, Bousquet J, Bateman ED. Improvement in asthma endpoints when aiming for total control: Salmeterol/fluticasone propionate versus fluticasone propionate alone. Prim Care Respir J [Internet]. 2007 [cited 2015 Aug 7];16(3):155-61. Available from: http://www.nature.com/articles/pcrj200743

54. Bateman ED, O'Byrne PM, Busse WW, Lotvall J, Bleecker ER, Andersen L, et al. Once-daily fluticasone furoate (FF)/vilanterol reduces risk of severe exacerbations in asthma versus FF alone. Thorax [Internet]. 2014 Apr [cited 2015 Sep 28];69(4):312-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3963539

55. Lin J, Kang J, Lee SH, Wang C, Zhou X, Crawford J, et al. Fluticasone furoate/vilanterol 200/25 mcg in Asian asthma patients: a randomized trial. Respir Med. 2015 Jan;109(1):44-53.

56. Yawn BP. Factors accounting for asthma variability: achieving optimal symptom control for individual patients. Prim Care Respir J. 2008 Sep;17(3):138-47.

57. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. J Allergy Clin Immunol. 2007 Nov;120(5 Suppl):S94-138.

58. Carranza R, Jr., Edwards L, Lincourt W, Dorinsky *P*, ZuWallack RL. The relationship between health-related quality of life, lung function and daily symptoms in patients with persistent asthma. Respir Med. 2004 Dec;98(12):1157-65.

59. Voorend-van Bergen S, Merkus *P*, Landstra A, Brackel H, van den Berg N, de Jongste J. Asthma-related quality of life in children: Correlation with asthma control and lung function [abstract]. Eur Respir J [Internet]. 2012 [cited 2015 Aug 12];40 Suppl 56. Available from: http://erj.ersjournals.com/content/40/Suppl_56/P4099.full.pdf+html

60. Ehrs PO, Aberg H, Larsson K. Quality of life in primary care asthma. Respir Med. 2001 Jan;95(1):22-30.

61. Moy ML, Israel E, Weiss ST, Juniper EF, Dube L, Drazen JM, et al. Clinical predictors of health-related quality of life depend on asthma severity. Am J Respir Crit Care Med. 2001 Mar;163(4):924-9.

62. Corre KA, Rothstein RJ. Assessing severity of adult asthma and need for hospitalization. Ann Emerg Med. 1985 Jan;14(1):45-52.

63. Enright PL, Beck KC, Sherrill DL. Repeatability of spirometry in 18,000 adult patients. Am J Respir Crit Care Med. 2004 Jan 15;169(2):235-8.

64. Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial? Eur Respir J. 1999 Jul;14(1):23-7.

65. Tepper RS, Wise RS, Covar R, Irvin CG, Kercsmar CM, Kraft M, et al. Asthma outcomes: pulmonary physiology. J Allergy Clin Immunol [Internet]. 2012 Mar [cited 2015 Sep 28];129(3 Suppl):S65-S87. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4263032

66. Yurdakul AS, Dursun B, Canbakan S, Cakaloglu A, Capan N. The assessment of validity of different asthma diagnostic tools in adults. J Asthma. 2005 Dec;42(10):843-6.

67. Hunter CJ, Brightling CE, Woltmann G, Wardlaw AJ, Pavord ID. A comparison of the validity of different diagnostic tests in adults with asthma. Chest. 2002 Apr;121(4):1051-7.

68. Eid N, Yandell B, Howell L, Eddy M, Sheikh S. Can peak expiratory flow predict airflow obstruction in children with asthma? Pediatrics. 2000 Feb;105(2):354-8.

69. Goldberg S, Springer C, Avital A, Godfrey S, Bar-Yishay E. Can peak expiratory flow measurements estimate small airway function in asthmatic children? Chest. 2001 Aug;120(2):482-8.

70. Dekker FW, Schrier AC, Sterk PJ, Dijkman JH. Validity of peak expiratory flow measurement in assessing reversibility of airflow obstruction. Thorax [Internet]. 1992 Mar [cited 2015 Aug 12];47(3):162-6. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1021004/pdf/thorax00363-0022.pdf

71. Ulrik CS, Postma DS, Backer V. Recognition of asthma in adolescents and young adults: which objective measure is best? J Asthma. 2005 Sep;42(7):549-54.

72. Karras DJ, Sammon ME, Terregino CA, Lopez BL, Griswold SK, Arnold GK. Clinically meaningful changes in quantitative measures of asthma severity. Acad Emerg Med. 2000 Apr;7(4):327-34.

73. Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the Asthma Quality of Life Questionnaire. Chest. 1999 May;115(5):1265-70.