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CADTH COMMON DRUG REVIEW

Clinical Review Report

FLUTICASONE PROPIONATE (AERMONY RESPICLICK)

(Teva Canada Innovation)

Indication: For the maintenance treatment of steroid-responsive bronchial asthma as prophylactic therapy in patients 12 years of age and older

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Abbreviations

ACT	Asthma Control Test
AE	adverse event
AQLQ(S)	Asthma Quality of Life Questionnaire With Standardized Activities
$AUC_{0-\infty}$	area under the curve from time zero extrapolated to infinite time
AUC_{0-t}	area under the curve from time zero up to the last measurable concentration
BMI	body mass index
CI	confidence interval
C_{max}	maximum measured concentration of analyte in plasma
CrI	credible interval
DB	double blind
DPI	dry powder inhaler
EMEA	European Medicines Agency
FAS	full analysis set
FEF	forced expiratory flow
FEV_1	forced expiratory volume in one second
Fp	fluticasone propionate
FVC	force vital capacity
HFA	hydrofluoroalkane
ICS	inhaled corticosteroid
ITT	intention to treat
LABA	long-acting beta-2 agonist
LOCF	last observation carried forward
LSM	least squares mean
LSMD	least squares mean difference
MDPI	multidose dry powder inhaler
MDI	metered-dose inhaler
MMRM	mixed model for repeated measures
pMDI	pressurized metered-dose inhaler
PP	per-protocol
PEF	peak expiratory flow
RCT	randomized controlled trial
RR	relative risk
SABA	short-acting beta-2 agonist
SAE	serious adverse event
SD	standard deviation
SE	standard error
WDAE	withdrawal due to adverse event

Drug	Fluticasone propionate (Aermony RespiClick)
Indication	For the maintenance treatment of steroid-responsive bronchial asthma as prophylactic therapy in patients 12 years of age and older
Reimbursement Request	As per indication
Dosage Form(s)	Dry powder for inhalation, available as 55 mcg, 113 mcg, and 232 mcg per actuation
NOC Date	August 22, 2017
Manufacturer	Teva Canada Innovation

Executive Summary

Introduction

Asthma is a common chronic respiratory disease involving inflammation of the airways.[1] It is characterized by symptoms such as wheezing, dyspnea, chest tightness, and cough, which are often associated with airflow limitation.[1] In 2016, 8.4% of Canadians 12 years and older were reportedly diagnosed with asthma by a health professional.[2]

Aermony RespiClick [fluticasone propionate (Fp) fine powder inhalation] is a twice-daily inhaled corticosteroid, which has been approved in Canada for the maintenance treatment of steroid-responsive bronchial asthma in patients 12 years and older.[3] Aermony RespiClick is administered by a multidose dry powder inhaler (MDPI) containing Fp for patients requiring inhaled corticosteroid (ICS) therapy. Fp is a corticosteroid with potent anti-inflammatory properties, specifically including inhibition of immune cells and mediator production or secretion. Fp has previously been approved for the treatment of asthma in other inhaled products within Canada, including Flovent Diskus, Flovent hydrofluoroalkane (HFA), and in the fixed-dose combination product with salmeterol xinafoate (Advair and Advair Diskus). The doses of Flovent Diskus (100 mcg, 200 mcg, 500 mcg) and Flovent HFA (50 mcg, 125 mcg, 250 mcg) are higher than those of Aermony RespiClick (55 mcg, 113 mcg, 232 mcg). The RespiClick delivery device is a breath-actuated, metered MDPI with the active ingredient dispersed in lactose monohydrate and contained within a reservoir. A metered dose of the drug is delivered to a dose cup through air pulse activation when the cap is opened. Upon inhalation, Fp is delivered to the airways as a fine powder.[4]

Another drug product proposed in conjunction with this version of Fp is Arbesda RespiClick (FS MDPI), in which Fp is combined with salmeterol xinafoate, a long-acting beta-agonist, is also delivered by MDPI. [redacted]

The objective of this review is to perform a systematic review of the beneficial and harmful effects of Fp MDPI 55 mcg, 113 mcg, and 232 mcg for the maintenance treatment of steroid-responsive bronchial asthma in patients 12 years and older.

Results and Interpretation

Included Studies

The evidence for this review was drawn from three multi-centre, randomized controlled trials, which met the criteria for inclusion in the systematic review: Study 301 (N = 647),[6] Study 30017 (N = 728),[7] and Study 305 (N = 674).[8] Two of the included studies (301 and 30017) were 12-week, placebo-controlled, double-blind, dose ranging, parallel-group trials designed to evaluate efficacy.[6,7] The third study (305) was a 26-week, open-label, active-comparator trial designed to evaluate safety.[8]

The two 12-week, double-blind placebo-controlled trials, studies 301 and 30017, were conducted in patients 12 years or older with persistent asthma who were not optimally controlled on their current low-, medium-, or high-dose ICS therapy.[6,7] The studies were identical in design; however, each assessed different Fp doses. In Study 301, patients were assigned to low-dose (55 mcg) Fp MDPI twice-daily, medium-dose (113 mcg) Fp MDPI twice-daily, or placebo; and in Study 30017, patients were assigned to medium-dose (113 mcg) Fp MDPI twice-daily, high-dose (232 mcg) Fp MDPI twice-daily, or placebo. The primary efficacy end point relevant to this review of an ICS for both trials was to demonstrate superiority of Fp MDPI at doses of 55 mcg, 113 mcg, and 232 mcg compared with placebo for a change from baseline in trough FEV_1 at week 12. Both studies also evaluated patient-reported outcomes as well as safety and tolerability in comparison with placebo. Salbutamol hydrofluoroalkane (or albuterol hydrofluoroalkane, depending on availability), a short-acting beta-2 agonist (SABA) inhaler, was provided to replace the patient's current rescue medication to be used as needed for symptomatic relief of asthma symptoms during the run-in and treatment periods. During the 14 to 21 day run-in period, patients discontinued their current ICS therapy and were switched to low-dose ICS (beclomethasone dipropionate [QVAR] 40 mcg HFA metered-dose inhaler [MDI] or Fp MDPI 55 mcg) until randomization to either Fp MDPI or placebo.[6,7]

The 26-week open-label safety trial, Study 305, was conducted in patients 12 years and older with an $FEV_1 \geq 40\%$ of predicted with an established treatment regimen of preventive asthma therapy for eight weeks or longer.[8] The objective of this study was to assess the safety of mid-strength (113 mcg) and high-strength (232 mcg) Fp delivered through MDPI compared with medium-strength (220 mcg) and high-strength (440 mcg) Fp delivered by hydrofluoroalkane (HFA) (Fp HFA). The primary end points in this study were the type and incidence of adverse events reported. Efficacy was not a primary or secondary objective in this study; however, investigators stated that the study had 90% power for demonstrating noninferiority between Fp MDPI and Fp HFA. Based on this assumption, the principal efficacy variable for this study was a change from baseline in trough FEV_1 over the treatment period, with a noninferiority margin pre-specified as –0.125 L.

There were a number of limitations noted with the included clinical trials. Firstly, the efficacy studies (studies 301 and 30017) are limited by their short duration of 12 weeks. The primary outcome in these studies was a change from baseline in trough FEV_1, which complements the short-term nature of the study; however, longer-term studies designed with more clinically important outcomes, such as exacerbations, would have been more informative. Also, in both efficacy studies the Fp MDPI dosage strengths were compared with placebo, rather than an active drug. Furthermore, there was a higher proportion of withdrawals in the placebo arms than in the Fp MDPI arms, which were generally due to worsening asthma. Sensitivity analyses were conducted on early withdrawal, which supported the primary efficacy end point conclusions; however, the potential for unblinding within patients in the placebo arms of these studies cannot be ruled out. With regard to the long-term safety

study, Study 305, the noninferiority comparisons for change from baseline in trough FEV_1 were hypothesized a priori for pooled arms of Fp MDPI and pooled arms of active comparator, Fp HFA; however, comparisons between the individual dosing arms were also reported. These comparisons do not appear to be adjusted for multiplicity, which would limit their interpretation. In addition, the choice of comparator in the safety Study 305 was questioned by the clinical expert consulted by CADTH. In this study, Fp MDPI was compared with the MDI version of Flovent, which was not used with a spacer. Without the use of a spacer with an MDI, errors in inhalation, and its resulting effects on reduced drug deposition of this comparator, cannot be ruled out.

Efficacy

In the 12-week studies 301 and 30017, all doses of Fp MDPI showed a statistically significant increase in change from baseline in trough FEV_1 at 12 weeks when compared with placebo. In Study 301, the difference from placebo in the change from baseline in trough FEV_1 for those taking 55 mcg was 0.119L ($P = 0.0132$) and for those taking 113 mcg it was 0.151 L ($P = 0.0017$). For the same outcome in Study 30017, the difference from placebo in those taking 113 mcg was 0.123 L ($P = 0.0047$) and in those taking 232 mcg it was 0.183 L ($P < 0.0001$). Little evidence is available on the minimal clinically important difference (MCID) for FEV_1. Secondary outcomes, such as the use of rescue SABA, Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ[S]), and asthma symptom scores were inconsistent in support of efficacy for the three doses compared with placebo.[6,7]

In the 26-week Study 305, all doses of Fp MDPI demonstrated noninferiority to Fp HFA for change from baseline in trough FEV_1. The lower limit of the 95% confidence interval exceeded the –0.125 L noninferiority margin for FEV_1 for all study drugs. The treatment differences at the different dose levels were 0.009 L (95% confidence interval [CI], –0.084 to 0.103) for Fp MDPI 113 mcg and –0.013 L (95% CI, –0.107 to 0.081) for Fp MDPI 232 mcg. Secondary outcomes of interest, such as AQLQ(S) and asthma symptom scores were not statistically different from the Fp HFA group. The change from baseline in trough FEV_1 in this study was lower than in studies 301 and 30017, possibly because patients in those studies were placed on low-dose ICS in the run-in period; whereas, in this study patients were not switched from their current asthma medications.[8]

An indirect treatment comparison was submitted by the manufacturer which compared the efficacy of Fp MDPI against similar treatments that are currently available.[9] The primary outcomes for this study were FEV_1, FEV_1 area under the curve, and asthma exacerbations. [redacted]

Harms

In studies 301 and 30017, the incidence of patients reporting any treatment-emergent adverse reactions was similar for Fp MDPI (range: 31% to 41%) and placebo (36%). The incidence of patients who had experienced a serious adverse event, or an adverse event causing withdrawal was less than 3% in any group. The most frequently reported adverse events across treatment groups were headache (4.8%), nasopharyngitis (4.5%), upper respiratory tract infection (4.1%), and oral candidiasis (2.3%). There were no deaths with placebo or Fp MDPI in either studies 301 or 30017.

In Study 305, the incidence of adverse events was comparable across treatment groups Fp MDPI and Fp HFA (66% to 71%). The most frequently occurring adverse event reported across all treatment groups were upper respiratory tract infections, nasopharyngitis, sinusitis, cough and oropharyngeal pain, and they were of mostly of mild or moderate severity. These are similar to the adverse events observed in studies 301 and 30017. Oral candidiasis was reported for ≤ 5% patients in the Fp MDPI groups and 12% in the Fp HFA 220 mcg group with no reports in the Fp HFA 110 mcg group. According the clinical expert in this study, this is usually dose-related, or device-related. There were no deaths reported in this study.

Other Considerations

The clinical studies (301, 30017, 305) included in this review evaluated both Fp MDPI (fluticasone propionate) and FS MDPI (fluticasone propionate/salmeterol xinafoate). In this systematic review, only the efficacy and safety of Fp MDPI was evaluated. The efficacy and safety of FS MDPI has been considered in a separate report.

Supportive data from two phase II dose-ranging studies were summarized (Appendix 8). The results of the studies indicated that Fp MDPI is not statistically significantly different from Flovent Diskus for the change in trough FEV_1 after 12 weeks of treatment. The studies were not designed to allow conclusions related to equivalence or noninferiority.

Conclusions

Three parallel-group randomized controlled trials that recruited patients 12 years and older with asthma, who were inadequately controlled on ICS were included in studies in which two different doses of Fp MDPI were compared against either placebo or Fp HFA for a minimum of 12 weeks and up to 26 weeks. There is limited comparative evidence for the use of Fp MDPI versus alternative ICS therapies. Consequently, no concrete conclusions can be drawn with respect to the comparative effects of Fp MDPI on asthma exacerbations.

Supportive data from two phase II dose-ranging studies suggested no statistically significant differences between Fp MDPI and Flovent Diskus for the change in trough FEV_1 over 12 weeks of treatment; however, this does not necessarily mean the Fp products are equivalent or noninferior to each other. Fp MDPI was found to be significantly superior to placebo with respect to pulmonary function. Results from the phase III efficacy studies suggest that compared with placebo, Fp MDPI 55 mcg, 113 mcg, and 232 mcg improved FEV_1 and increased the number of days without asthma symptoms through 12 weeks. Fp MDPI may improve quality of life relative to placebo; however, the effect was inconsistent across studies. No rigorous assessment of patient preferences regarding the Fp MDPI inhaler in comparison with other available devices in this patient population was identified.

Studies were limited by their duration (12 to 26 weeks) because of the reduced evidence requirements for this second entry product. Nevertheless, considering the chronic use of ICS in patients with asthma, the submitted direct and indirect data do not provide evidence for the longer-term effects of FP MDPI; longer-term comparative studies would be useful to elucidate the efficacy and harms of Fp MDPI beyond 26 weeks of exposure.

Table 1: Summary of Key Efficacy Results From Placebo-Controlled Trials

End Points	Study 301			Study 30017		
	Placebo	Fp MDPI 55 mcg b.i.d.	FP MDPI 113 mcg b.i.d.	Placebo	Fp MDPI 113 mcg b.i.d.	Fp MDPI 232 mcg b.i.d.
Change in trough FEV_1 at 12 weeks						
N	129	128	129	143	144	145
Baseline (SE)	2.188 (0.0496)	2.132 (0.0558)	2.166 (0.0504)	2.132 (0.0568)	2.069 (0.500)	2.075 (0.0471)
LS mean (SE)	0.053 (0.0350)	0. 172 (0.0347)	0.204 (0.0340)	–0.004 (0.0312)	0.119 (0.0311)	0.179 (0.0308)
LSMD (95% CI) versus PBO[b]	—	0.119[a] (0.025 to 0.212)	0.151[a] (0.057 to 0.244)	—	0.123[a] (0.038 to 0.208)	0.183[a] (0.098 to 0.268)
P value	—	0.0132	0.0017	—	0.0047	0.0000
Change in weekly average of the total daily asthma symptom scores at week 12 or end point						
N	128	128	129	142	145	146
Baseline (SE)	0.796 (0.0356)	0.825 (0.0423)	0.782 (0.0395)	0.881 (0.0470)	0.804 (0.0409)	0.900 (0.0424)
LS mean	–0.135 (0.0318)	–0.278 (0.0314)	–0.300 (0.0308)	–0.087 (0.0342)	–0.282 (0.0333)	–0.242 (0.0329)
LSMD (95% CI) vs. PBO[b]	—	–0.143 (–0.229 to –0.058)	–0.165[a] (–0.251 to –0.080)	—	–0.195[a] (–0.288 to –0.102)	–0.156[a] (–0.248, to –0.063)
Change from baseline weekly mean number of inhalations of rescue medication (albuterol or salbutamol) per 24 hours at week 12 or end point						
N	129	128	129	143	145	146
Baseline number of inhalations (SE)	1.4 (0.11)	1.3 (0.10)	1.2 (0.11)	1.7 (0.15)	1.6 (0.13)	1.8 (0.13)
LS mean	–0.003 (0.0937)	–0.467 (0.0928)	–0.466 (0.0915)	0.168 (0.1102)	–0.439 (0.1081)	–0.534 (0.1070)
LSMD (95% CI) versus PBO[b]	—	–0.464 (–0.718 to –0.211)	–0.463[a] (–0.716 to –0.209)	—	–0.607[a] (–0.908 to –0.307)	–0.702[a] (–1.001 to –0.403)
Change from baseline in AQLQ(S) at week 12 or end point						
N	97	108	103	101	126	125
Baseline (SE)	4.921 (0.0958)	5.151 (0.0975)	5.025 (0.0799)	4.924 (0.0794)	5.024 (0.0820)	4.941 (0.0796)
LS mean	0.335 (0.0777)	0.588 (0.0733)	0.636 (0.0736)	0.203 (0.0761)	0.334 (0.0683)	0.418 (0.0685)
LSMD (95% CI) versus PBO[b]	—	0.253 (0.048 to 0.458)	0.301[a] (0.094, 0.508)	—	0.131 (–0.068 to 0.330)	0.216[a] (0.017 to 0.415)

AQLQ(S) = Asthma Quality of Life Questionnaire With Standardized Activities; b.i.d. = twice daily; CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; Fp MDPI = fluticasone propionate multidose dry powder inhaler; LS = least squares; LSMD = least squares mean difference; PBO = placebo; SE = standard error.

[a] Statistically significant results.

[b] LS mean adjusted in the ANCOVA model with baseline value, sex, age, (pooled) centre, previous therapy (ICS or ICS/LABA), and treatment as covariates.

Source: Clinical Study Reports.[6,7]

Introduction

Disease Prevalence and Incidence

Asthma is a common chronic respiratory disorder characterized by reversible airway obstruction, pulmonary inflammation, airway hyper-responsiveness, and airway remodelling.[10,11] Described by a range of heterogeneous phenotypes, symptoms may differ by presentation, etiology, and pathophysiology. Patients with asthma typically present with paroxysmal or persistent symptoms of wheezing, dyspnea, chest tightness, sputum production, and coughing that are associated with airflow limitation and airway hyper-responsiveness to endogenous and exogenous stimuli (e.g., exercise; viral respiratory infections; or exposure to certain allergens, irritants, or gases).[11] Although asthma can be diagnosed at any age, it often starts in childhood. In 2015, Statistics Canada estimated that 2.4 million Canadians 12 years and older had a diagnosis of asthma,[12] representing 12% of all Canadian children and 8% of all Canadian adults.[12]

Standards of Therapy

Given its heterogeneous phenotypes, the treatment for asthma is individualized to each patient's unique circumstances and customized as necessary. The primary goals to asthma management include long-term maintenance of asthma control[11] with the least amount of medication and minimization of adverse events.[13] Asthma control, in the Canadian Thoracic Society guidelines, is based on several characteristics including:

- frequency of daytime and nighttime symptoms
- frequency of exacerbations
- the frequency of absences from work or school due to asthma
- the ability to complete normal physical activity
- the need for a fast-acting beta-2 agonist
- forced expiratory volume in one second (FEV_1) or peak expiratory flow (PEF)
- PEF diurnal variation
- sputum eosinophils.[11]

Asthma control may prevent or minimize the risks to short- and long-term complications, further morbidity, and death.[11] It has been reported that much of asthma-related morbidity is associated with poor management from underused therapy or poor adherence to maintenance therapy.[14]

According to the guidelines published by the Canadian Thoracic Society, a stepwise approach to pharmacological therapy is recommended to achieve and maintain asthma control.[11] This involves escalating pharmacological treatment, as necessary, to gain control (i.e., step up) and then reducing treatment (i.e., step down) to the minimum required with respect to dose and number of medications for maintenance.[11] Current Canadian and international guidelines recommend that patients with asthma in all age groups be initiated with low-dose inhaled corticosteroids (ICS).[11,15] If control is not gained or maintained, second-line drugs may be added, such as a long-acting beta-2 agonist (LABA) or leukotriene receptor antagonists, or the ICS dose can be titrated upward.[11]
Table 2 provides a list of ICS available in Canada.

Drug

Aermony RespiClick (fluticasone propionate [Fp]) is indicated for the maintenance treatment of steroid-responsive bronchial asthma as prophylactic therapy in patients 12 years and older.[3] It is available as a dry powder delivered via metered-dose inhaler with three dosage strengths that deliver 55 mcg, 113 mcg, or 232 mcg Fp twice-daily.[6] According to the product monograph for Fp, initial recommended doses should be based on patient's asthma severity. For patients switching from another ICS product, the product monograph advises to begin at a low (55 mcg), medium (113 mcg) or high (232 mcg) dose strength based on both their previous ICS product strength (i.e., low-, medium-, or high-dose) and their level of disease severity.[3] Each inhaler contains 60 actuations.[6] This Fp preparation contains a lower nominal dose than other existing Fp preparations, and pharmacokinetic studies suggest that the systemic exposure of these products are lower or similar with Fp as compared with Flovent Diskus or Flovent HFA.[16,17] For Fp, following a single inhalation of 232 mcg (high dose based on the product monograph), the exposure (C_{max} and area under the curve) of Fp was approximately 20% to 30% lower compared with a 500 mcg dose (considered high dose based on the product monograph) of Flovent Diskus.[16,18]

Table 2: Key Characteristics of Inhaled Corticosteroids Monotherapies for Bronchial Asthma

	Fluticasone Propionate (AERMONY RESPICLICK[3])	Fluticasone Propionate (FLOVENT DISKUS/HFA[18])	Fluticasone Furoate (ARNUITY ELLIPTA[19])	Mometasone Furoate (ASMANEX[20])	Ciclesonide (ALVESCO[21])	Budesonide (PULMICORT[22])	Beclomethasone (QVAR[23])
Mechanism of action	Glucocorticoid anti-inflammatory steroid.	Glucocorticoid anti-inflammatory steroid.	Synthetic trifluorinated corticosteroid. Precise mechanism in which asthma symptoms are affected is unknown.	A corticosteroid demonstrating anti-inflammatory properties. Precise mechanism of corticosteroid action on asthma unknown.	It has an active glucocorticoid metabolite that binds to glucocorticoid receptors in the lung resulting in local anti-inflammatory activity.	Synthetic glucocorticoid with strong topical and weak systemic effects.	Synthetic corticosteroid, topical anti-inflammatory agent at deposition site of bronchial tree.
Health Canada-approved indication	Maintenance treatment of steroid-responsive bronchial asthma as prophylactic therapy in patients 12 years and older.	Prophylactic management of steroid-responsive bronchial asthma in adults and children (12 months of age and older).	Maintenance treatment of steroid-responsive bronchial asthma in patients aged 12 years and older.	Prophylactic management of steroid-responsive bronchial asthma in patients 4 years of age and older.	Prophylactic management of steroid-responsive bronchial asthma in adults, adolescents, and children 6 years of age and older.	For patients 6 years and older with bronchial asthma who require inhaled steroids and in those for whom reduction of systemic glucocorticoids is desirable.	Prophylactic management of steroid-responsive bronchial asthma in patients 5 years and older.
Route of administration	Oral inhalation						
Recommended dose	Starting dosages based on asthma severity and response. When switching from another ICS product, select low, medium or high-strength based on previous ICS dose and level	Dose depends on asthma severity and patients 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.	100 mcg to 200 mcg q.d.	<12 years: 100 mcg q.d. ≥12 years: 200 mcg q.d., 200 mcg b.i.d., or 400 mcg q.d.	6 to 11 years: 100 mcg to 200 mcg q.d. ≥ 12 years: 400 mcg q.d. (dose range is 100 to 800 mcg)	Starting dose[b]: 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. The maintenance dose is 200 to	5 to 11 years old: 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

		Fluticasone Propionate (AERMONY RESPICLICK[3])	Fluticasone Propionate (FLOVENT DISKUS/HFA[18])	Fluticasone Furoate (ARNUITY ELLIPTA[19])	Mometasone Furoate (ASMANEX[20])	Ciclesonide (ALVESCO[21])	Budesonide (PULMICORT[22])	Beclomethasone (QVAR[23])
		of asthma severity: Low: 55 mcg b.i.d. Medium: 113 mcg b.i.d. High: 232 mcg b.i.d.					400 mcg b.i.d.	b.i.d. Severe: 300 mcg to 400 mcg b.i.d.
		The lowest dose required to maintain good asthma control should be used						
Serious side effects / safety issues (as reported in product monographs)		Thrush, infections, allergic reactions, hypercorticism and adrenal suppression, reduction in bone mineral density, slowed growth in children, and glaucoma and cataracts.	Thrush, allergic reactions, Chug-Straus Syndrome, esophageal candidiasis, slowed growth in children and adolescents, and Cushing's Syndrome.	Thrush, bronchitis, pneumonia, asthma exacerbations, decreased adrenal functions, glaucoma, cataract, allergic reaction, and bone fractures or osteoporosis.	Thrush, serious allergic reactions, worsening asthma or sudden asthma attack, increase heart rate, respiratory distress, Chug-Straus Syndrome, glaucoma, cataract, or decreased adrenal function.	Sudden wheeziness and chest pain or tightness.	Bronchospasm and severe allergic reactions.	No serious adverse events were signalled in the product monograph[23]
		In general, inhaled corticosteroid therapy may be associated with dose-dependent increases in the incidence of ocular complications, reduced bone density, suppression of hypothalamic-pituitary-adrenal axis responsiveness to stress, and inhibition of growth velocity in children.						
Dose equivalence	**High**	Not available[b]	> 500 mcg to 100 mcg	200 mcg	≥ 800 mcg	> 320 mcg to 1,280 mcg	> 800 mcg to 1,600 mcg	> 1,000 mcg to 2,000 mcg
	Med		> 250 mcg to 500 mcg	100 mcg	≥ 400 mcg	> 160 mcg to 320 mcg	> 400 mcg to 800 mcg	> 500 mcg to 1,000 mcg
	Low		**100 mcg to 250 mcg**		**200 mcg**	**80 mcg to 160 mcg**	**200 mcg to 400 mcg**	200 mcg to 500 mcg

b.i.d. = twice daily; mcg = microgram; HFA = hydrofluoroalkane; ICS = inhaled corticosteroid; q.d. = once daily.

[a] During severe asthma and while reducing or discontinuing oral glucocorticoids.

[b] Steroid equivalencies have not yet been published. The product monograph suggests 55 mcg as low dose, 113 mcg as medium dose, and 232 mcg as high dose.

Source: Product Monographs.[3,18-23]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of fluticasone propionate (Aermony RespiClick) for the twice-daily maintenance treatment of steroid-responsive bronchial asthma as prophylactic therapy in patients 12 years of age and older.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the manufacturer's submission to the CADTH Common Drug Review and Health Canada, as well as those meeting the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient Population	Patients (≥ 12 years of age) with steroid-responsive bronchial asthma
Intervention	Fluticasone propionate (55 mcg, 113 mcg, or 232 mcg); oral inhalation twice-daily (+/- SABA)
Comparators	Inhaled corticosteroids (+/- SABA)
Outcomes	**Key efficacy outcomes:** • Acute exacerbations of asthma • Change in pulmonary function[a] (i.e., FEV_1) • Health-related quality of life[a] • Control of asthma symptoms • Use of rescue medications • Dyspnea • Nocturnal awakening **Other efficacy outcomes:** • Days of missed work/school • Patient adherence to regimen[a] • Ease of use[a] • Health care resource utilization (e.g., hospitalizations, ED visits, physician visits) **Harms outcomes:** • Mortality • SAEs • WDAEs • AEs • Notable harms: infections (systemic and local), steroid effects (topical, systemic), growth rates (12 to 17 year age group), adrenal suppression
Study Design	Published and unpublished RCTs, phase III or IV

AE = adverse event; ED = emergency department; FEV_1 = forced expiratory volume in 1 second; RCT = randomized controlled trial; SABA = short-acting beta-2 agonists; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Key outcomes identified from the patient group input to CADTH.

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 ALL (1946-) through Ovid; Embase (1974-) through 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 Aermony RespiClick (fluticasone propionate), asthma, and dry powder inhaler.

No methodological filters were applied to limit retrieval to study type. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on March 5, 2018. Regular alerts were established to update the search until the meeting of CADTH's Canadian Drug Expert Committee on July 18, 2018. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, databases (free), and Internet search. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 16; excluded studies (with reasons) are presented in Table 38.

Results

Findings From the Literature

A total of three studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and Table 5, and further described in the Included Studies section. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

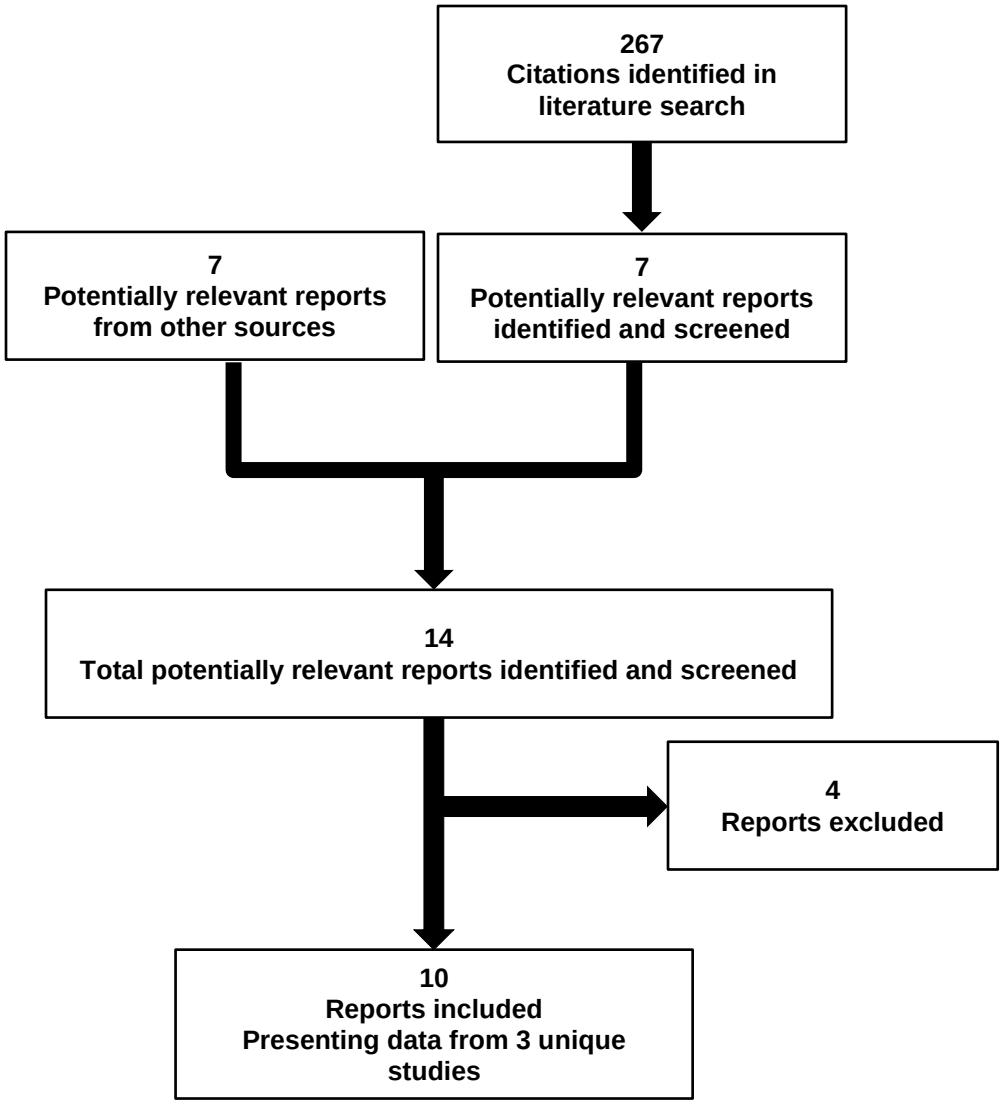


Table 4: Details of Included Efficacy Studies

		FSS-AS-301	FSS-AS-30017
Designs and Populations	**Study Design**	12-week, double-blind, phase III, multi-centre, placebo-controlled RCT	
	Locations	129 centres in the US, Canada, Czech Republic, Hungary, Poland, Russia, South Africa, and Ukraine	147 centres in US, Canada, Czech Republic, Hungary, Poland, Russia, South Africa, and Ukraine
	Randomized (N)	647	728
	Inclusion Criteria	• ≥ 12 years of age with persistent asthma as defined by the National Institute of Health[24] • FEV_1 ≥ 40% and ≤ 85% of predicted values for age, height, sex, and race • Diagnosis of asthma for ≥ 3 months with no exacerbations or changes to asthma medications for at least 30 days • Ability to perform repeatable spirometry consistent with ATS/ERS 2005 criteria[25] • Prior treatment with ICS or ICS/LABA for ≥ 1 month at qualifying dosage (Table 6). If on ICS/LABA must have prescreening visit to change to ICS monotherapy and stable for one month • Able to withhold all inhaled ICS and SABA medication for ≥ 6 hours prior to study visits • Ability to use MDI device without a spacer device and an MDPI device • ≥ 15% reversibility for all patients (and ≥ 200 mL increase for those ≥ 18 years from baseline FEV_1) within 30 minutes following two to four inhalations of albuterol/salbutamol	
	Exclusion Criteria	• History of life-threatening asthma exacerbation • Any of the following before screening: asthma exacerbation requiring systemic corticosteroids (within 30 days); hospitalization for asthma (within 2 months); immunosuppressive medications (within 4 weeks) • Initiation or dose escalation of immunotherapy planned during the study period • Bacterial or viral infection of the upper or lower respiratory tract, sinus, or middle ear (within two weeks) • Current smokers, those with a smoking history of ≥ 10 pack-years, or use of any tobacco products within the past year	
Drugs	**Interventions**	• Fp MDPI 55 mcg b.i.d. • Fp MDPI 113 mcg b.i.d. • FS MDPI 55 mcg/12.5 mcg b.i.d. • FS MDPI 113 mcg/12.5 mcg b.i.d.	• Fp MDPI 113 mcg b.i.d. • Fp MDPI 232 mcg b.i.d. • FS MDPI 113 mcg/12.5 mcg b.i.d. • FS MDPI 232 mcg/12.5 mcg b.i.d.
	Comparator	• Placebo	• Placebo
Duration	**Phase**		
	Run-in	14 to 21 days	
	Double blind	12 weeks	
	Follow-up	5 to 9 days	
Outcomes	**Primary End Points**	• Change from baseline in trough FEV_1 at 12 weeks • FEV_1 from 0 to 12 hours post-dose at 12 weeks (FEV_1 $AUC_{0\text{-}12h}$) in serial spirometry subset	
	Other End Points	• Trough morning peak expiratory flow • Asthma symptom score • Rescue medication usage • Withdrawal due to worsening asthma • AQLQ(S) (≥ 18 years of age only) • Time to 15% and 12% improvement in FEV_1 (serial spirometry subset) • Asthma Control Test • Symptom-free and rescue-free days	
Notes	**Publications**	Raphael et al., 2017[26]	Sher et al., 2016[27]

ATS/ERS = American Thoracic Society/European Respiratory Society Task Force; AQLQ(S) = Asthma Quality of Life Questionnaire with Standardized Activities; AUC = area under curve; b.i.d. = twice-daily; FEV_1 = forced expiratory volume in 1 second; FEV_1 $AUC_{0\text{-}12h}$ = forced expiratory volume in 1 second from time 0 to 12 hours post-dose; Fp = fluticasone propionate; FS = fluticasone propionate/ salmeterol xinofoate; ICS = inhaled corticosteroid; LABA = long-acting beta-agonist; MDPI = multidose dry powder inhaler; MDI = metered-dose inhaler; RCT= randomized controlled trial; SABA = short-acting beta-2 agonist.

Note: Four additional reports were included (Manufacturer's submission to CDR,[28] Health Canada Reviewer's report,[2] and the FDA Medical and Statistical review reports[4,29]).

Source: Clinical study reports,[6,7] Raphael et al., 2017,[26] Sher et al., 2016.[27]

Table 5: Details of Included Safety Study

		FSS-AS-305
Designs and Populations	**Study Design**	26-week, open-label, phase III, safety RCT
	Locations	103 centres
	Randomized (N)	674
	Inclusion Criteria	• Age ≥ 12 years • FEV_1 of ≥ 40% of predicted • Established treatment regimen of a SABA and either a mid- or high-dose ICS or ICS/ LABA combination as preventive therapy for ≥ 8 weeks • Reversibility of disease (≥ 12% reversibility for all patients and ≥ 200 mL increase for those ≥ 18 years from baseline FEV_1) within 30 minutes following two to four inhalations of albuterol/salbutamol • Diagnosis of asthma present for ≥ 3 months with no exacerbations or changes in medications for at least one month • Ability to perform repeatable spirometry consistent with ATS/ERS 2005 criteria[25] • Ability to use an MDI device without a spacer device and a MDPI device • Able to withhold inhaled ICS and SABA medication for ≥ 6 hours prior to study visits
	Exclusion Criteria	• History of life-threatening asthma exacerbation • Any of the following before screening: asthma exacerbation requiring systemic corticosteroids (within 30 days); hospitalization for asthma (within 2 months); immunosuppressive medications (within 4 weeks) • Initiation or dose escalation of immunotherapy planned during the study period • Bacterial or viral infection of the upper or lower respiratory tract, sinus, or middle ear (within two weeks) • Current smokers, had a smoking history of ≥ 10 pack-years, or had used any tobacco products within the past year
Drugs	**Interventions**	• Fp MDPI 113 mcg b.i.d. • Fp MDPI 232 mcg b.i.d. • FS MDPI 113 mcg/12.5 mcg b.i.d. • FS MDPI 232 mcg/12.5 mcg b.i.d.
	Comparators	• Flovent HFA 110 mcg b.i.d. • Flovent HFA 220 mcg b.i.d. • Advair Diskus 250 mcg /50 mcg b.i.d. • Advair Diskus 500 mcg/50 mcg b.i.d.
Duration	**Phase**	
	Run-in	12 to 16 days
	Double blind	26 weeks
	Follow-up	5 to 9 days
Outcomes	**Primary End Point**	Incidence and type of all adverse events
	Other End Points	• Trough FEV_1 over 26 weeks (principal efficacy variable) • Severe asthma exacerbations • Rescue medication use • Symptom-free and rescue-free days • Withdrawal due to worsening asthma • Asthma symptom scores • Health care resource utilization • Antibiotic usage
Notes	**Publications**	• Mansfield et al., 2017[30]

AQLQ(S) = Asthma Quality of Life Questionnaire with Standardized Activities; ATS/ERS = American Thoracic Society/European Respiratory Society Task Force; AUC = area under curve; b.i.d. = twice daily; FEV_1 = forced expiratory volume in 1 second; FEV_1 $AUC_{0\text{-}12h}$ = forced expiratory volume in 1 second from time 0 to 12 hours post-dose; Fp= fluticasone propionate; FS= fluticasone propionate/ salmeterol xinofoate; ICS= inhaled corticosteroid; LABA= long-acting beta-agonist; MDPI = multidose dry powder inhaler; SABA= short-acting beta-2 agonist.

Note: Four additional reports were included (Manufacturer's submission to CDR,[28] Health Canada Reviewer's report,[2] and the FDA Medical and Statistical review reports[4,29]).

Source: Clinical study report,[8] Mansfield et al., 2017.[30]

Included Studies

Description of Studies

Efficacy Trials

Figure 2 provides an overview of the two trials designed to evaluate efficacy. Studies 301 and 30017 were both multi-centre, multinational, phase III, five-arm, double-blind, placebo-controlled RCTs. Both trials included two Fp MDPI (multidose dry powder inhaler) treatment groups (55 mcg twice daily or 113 mcg twice daily in Study 301, and 113 mcg twice daily or 232 mcg twice daily in Study 30017), two FS MDPI groups (55 mcg/12.5 mcg twice daily or 113 mcg/12.5 mcg twice daily in Study 301, and 113 mcg/12.5 mcg twice daily or 232 mcg/12.5 mcg twice daily in Study 30017), and a matching placebo group. Patients were randomized (1:1:1:1:1) to receive one of the active treatments or placebo using an interactive response technology. Randomization was not reported to have been stratified by any variables. Patients, investigators, and clinical personnel were blinded to the treatment assignment during the study. The Arbesda RespiClick (FS MDPI) arms of this study were not reported in this review, as they are to be covered in full detail in a separate review.

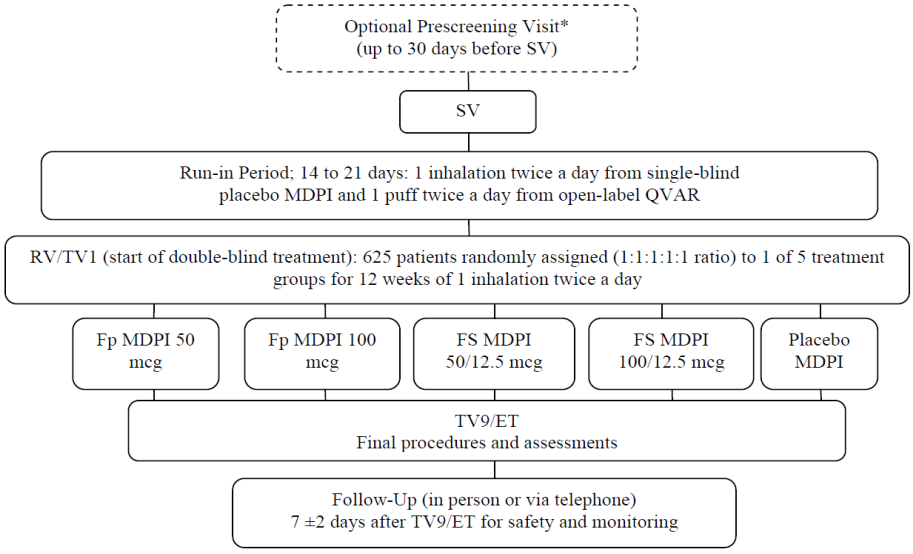
Before randomization, patients who met all of the eligibility criteria at the screening visit entered into a 14 to 21 day run-in period where they discontinued their current ICS therapy and were administered the following treatments: one inhalation of single-blinded Fp MDPI 55 mcg twice a day (Study 30017); or one inhalation twice a day of a single-blinded placebo MDPI device and one inhalation twice a day of open-label beclomethasone dipropionate (QVAR 40 mcg HFA metered-dose inhaler [MDI]) or equivalent (Study 301). In both trials, patients were provided with albuterol/salbutamol hydrofluoroalkane (HFA) (MDI) to replace their current rescue medication. The manufacturer reported that the intent of the run-in period was to evaluate adherence and complete baseline evaluations for safety, asthma symptoms, and use of rescue medication. In addition, patients were provided with training on the use of the MDPI device at every treatment visit except for the final treatment visit, as well as during screening. Ability to use an MDPI device was listed as a criterion for inclusion for both studies.

Patients were required to attend a screening visit, randomization visit, eight study visits during the double-treatment period (one per week), and a follow-up visit after the end of treatment. Patients recorded the following information in diaries: daytime and nighttime asthma symptoms, use of rescue medication, adherence with the study treatments, health-related events, and changes in medication.

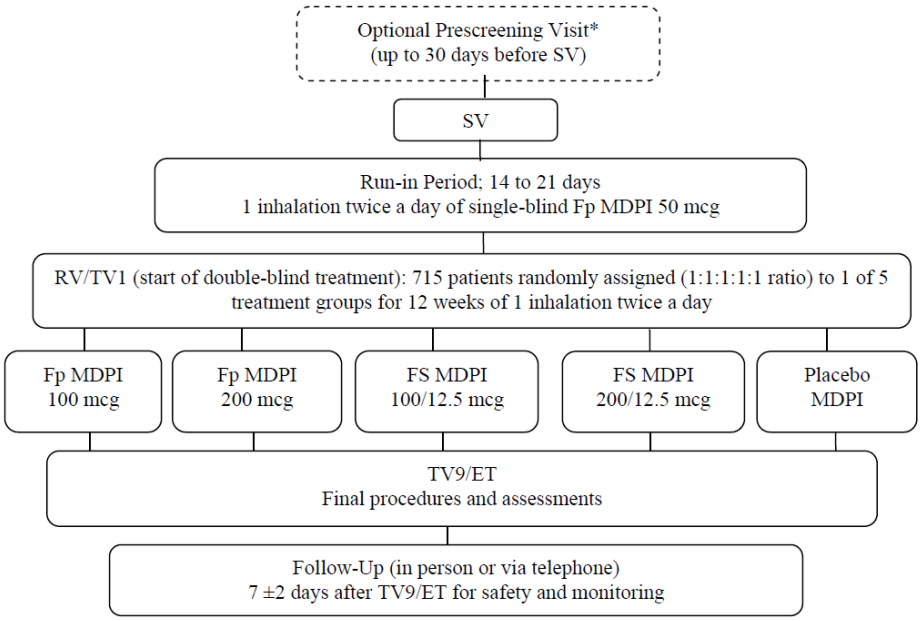
A subset of patients who performed serial spirometry were included in the studies; however, following discussion with the clinical expert involved in the review, this subpopulation was not considered for this review.

Figure 2: Design of Efficacy Trials

A: Design for Study 301



B: Design for Study 30017



ET = early termination; Fp = fluticasone propionate; FS = fluticasone propionate/salmeterol xinafoate; MDPI = multidose powdered inhaler; RV = randomization visit; SV = screening visit; TV = treatment visit.

Note: Dosing of Fp MDPI and FS MDPI were referred to in the figures above by their nominal doses. Their metered doses are 55 mcg, 113 mcg, and 232 mcg for Fp MDPI, and 55 mcg/12.5 mcg, 113 mcg/12.5 mcg and 232 mcg/12.5 mcg for FS MDPI. These products have been referred to by their metered doses in this report.

* Required for patients whose pre-study asthma therapy included a LABA in addition to ICS therapy.

Source: Clinical study reports.[6,7]

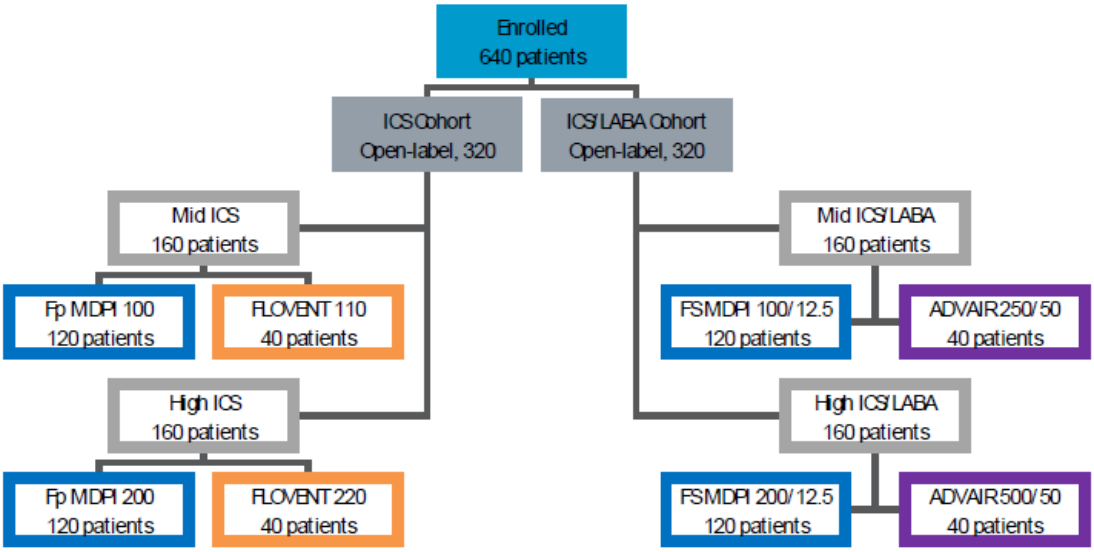
Safety Trial

Figure 3 provides an overview of the long-term safety trial. Study 305 was an eight-arm, 26-week, open-label, active-controlled, phase III RCT designed to evaluate safety. Before screening, patients were assigned to one of four treatment categories (medium-strength ICS monotherapy, high-strength ICS monotherapy, medium-strength ICS/LABA combination therapy, and high-strength ICS/LABA combination therapy) based on their existing asthma regimen. Patients in the mid-strength ICS monotherapy category were randomized 3:1 to receive Fp MDPI 113 mcg twice daily or two puffs of Fp HFA (Flovent HFA) 110 mcg twice daily. Patients in the high-strength ICS monotherapy category were randomized 3:1 to Fp MDPI 232 mcg twice daily or two puffs of Fp HFA 220 mcg twice daily. Randomization was not reported to have been stratified by any variables. Patients previously taking mid-strength ICS/LABA monotherapy category were randomized 3:1 to FS MDPI 113 mcg/12.5 mcg twice daily or Advair Diskus 250 mcg/50 mcg twice daily. Patients previously taking high-strength ICS/LABA monotherapy were randomized 3:1 to FS MDPI 232 mcg/12.5 mcg twice daily or Advair Diskus 500 mcg/50 mcg twice daily.[8] As with the efficacy studies 301 and 30017, the FS MDPI arms of this study were not reported in this review, since they will be covered in full detail in a separate review.

Eligible patients entered into a 14-day (± 2 days) run-in period where they were instructed to continue using their current ICS and/or controller therapies, except for their short-acting beta-2 agonist inhaler (to be used as needed for symptomatic relief of asthma symptoms), which was replaced with salbutamol/albuterol. As a result, patients did not discontinue their current ICS or ICS/LABA treatment until randomization.

Patients were required to attend a screening visit, randomization visit, eight study visits during the double-treatment period (once every four weeks), and a follow-up visit after the end of treatment. Patients recorded the following information in diaries: daytime and nighttime asthma symptoms, use of rescue medication, compliance/adherence with the study treatments, health-related events, and changes in medication.

Figure 3: Design of Safety Trial (Study 305)



FS = fluticasone propionate/salmeterol xinafoate; ICS = inhaled corticosteroid; LABA = long-acting beta-adrenoceptor agonist; MDPI = multidose dry powder inhaler.

Note: Dosing of Fp MDPI and FS MDPI were referred to in the figures above by their nominal doses. Their metered doses are 55 mcg, 113 mcg, and 232 mcg for Fp MDPI, and 55 mcg/12.5 mcg, 113 mcg/12.5mcg and 232 mcg/12.5 mcg for FS MDPI. These products have been referred to by their metered doses in this report.

Source: Clinical study report.[8]

Populations

Inclusion and Exclusion Criteria

Efficacy Trials

Screening eligibility criteria was similar in both studies 301 and 30017, with the exception of the qualifying therapies of treatment. Study 301 aimed to include patients taking low or medium-dose ICS monotherapy or ICS/LABA combination at least one month before providing consent; whereas, Study 30017 aimed to include patients taking medium- or high-dose ICS monotherapy or ICS/LABA at least one month before providing consent. Qualifying dosages of previous ICS and ICS/LABA regimens are summarized in Table 6. Inclusion criteria common among both studies were that patients were at least 12 years of age, with forced expiratory volume in one second (FEV_1) of at least 40% and less than or equal to 85% of predicted, with demonstrated reversibility of at least 15% and at least a 200 mL increase from baseline FEV_1 (for patients at least 18 years of age) within 30 minutes after two to four inhalations of albuterol/salbutamol HFA MDI or the equivalent at screening. It was also required that a patient have a diagnosis of asthma as defined by the National Institute of Health (NIH),[24] that the diagnosis of asthma be present for a minimum of three months, and that no asthma exacerbations or changes in asthma medication occurred for at least 30 days before the informed consent was signed.

Table 6: Qualifying Therapies for Efficacy Trials

Qualifying ICS or ICS/LABA	Daily Dosage (mcg)	
	Study 301	Study 30017
Fluticasone HFA	88 to 500	> 200
Fluticasone DPI	50 to 500	> 200
Budesonide HFA (80 mcg/dose or 160 mcg/dose)	80 to 480	> 160
Budesonide HFA (100 mcg/dose or 200 mcg/dose)	100 to 400	> 200
Budesonide DPI	90 to 720	> 200
Beclomethasone dipropionate HFA small particle	40 to 240	> 160
Beclomethasone dipropionate HFA large particle	50 to 400	> 300
Mometasone DPI	110 to 440	> 220
Mometasone pMDI	200 to 400	> 200
Ciclesonide HFA	80 to 240	> 160
Flunisolide pMDI	320 to 480	> 320
Fluticasone/salmeterol HFA	90 to 500	> 200
Fluticasone/salmeterol DPI	100 to 500	> 200
Budesonide/formoterol MDI	80 to 480	> 160
Budesonide/formoterol DPI	100 to 400	> 200

ICS = inhaled corticosteroid; LABA = long-acting beta 2-agonist; HFA = hydrofluoroalkane; DPI = dry powder inhaler;

MDI = metered-dose inhaler; pMDI = pressurized metered-dose inhaler.

Source: Clinical study report.[6,7]

Safety Trial

Patients were included in the study if they were a male or female 12 years of age or older at the time informed consent was signed, and suffering from persistent asthma with an $FEV_1 \geq 40\%$ of the value predicted for age, height, sex, and race, and unlike the efficacy studies 301 and 30017, the safety trial did not specify an upper limit for FEV_1. Patients were required to have a treatment regimen that included a SABA (salbutamol) for use as needed and either an ICS or an ICS/LABA as a preventive treatment for a minimum of eight weeks before screening. Patients currently taking low-dose ICS without LABA were not eligible for this study. Patients currently taking low-dose ICS/LABA could only be entered into the medium ICS strength. All patients were required to have been maintained on a stable dose of ICS or ICS/LABA for four weeks before the screening visit at one of the qualifying doses summarized in Table 7. Lastly, patients were required to demonstrate a ≥ 12% reversibility of FEV_1 (and 200 mL for patients 18 years and older) within 30 minutes following four inhalations of salbutamol HFA at the screening visit.

Patients were excluded from participating in this study if one or more of the following main criteria were met (not all inclusive): history of a life-threatening asthma exacerbation requiring intubation and/or associated with hypercapnia, respiratory arrest, or hypoxic seizures; pregnancy or lactation; or participation as a randomized patient in any investigational drug study within the 30 days preceding the screening visit or planned participation in another investigational drug study at any time during this study.

Table 7: Qualifying Therapies for the Safety Trial

Qualifying ICS or ICS/LABA	Daily Dosage (mcg)
Permitted Low-Strength ICS/LABA Medications or Equivalent	
Fluticasone/salmeterol HFA	180
Fluticasone/salmeterol DPI	200
Budesonide/formoterol HFA	160 to 240
Mometasone/formoterol pMDI	200
Permitted Medium-Strength Medications or Equivalent	
Fluticasone HFA	> 180 to 460
Fluticasone DPI	> 200 to 500
Budesonide HFA	> 240 to 480
Budesonide DPI	> 180 to 720
Beclomethasone dipropionate HFA small particle	> 160 to 240
Ciclesonide	160 to 240
Mometasone pMDI	> 200 to 400
Mometasone DPI	> 220 to 440
Permitted High-Strength Medications or Equivalent	
Fluticasone HFA	> 460
Fluticasone DPI	> 500
Budesonide HFA	> 480
Budesonide DPI	> 720
Beclomethasone dipropionate HFA small particle	> 240
Ciclesonide	> 240
Mometasone pMDI	> 400
Mometasone DPI	> 440

DPI = dry powder inhaler; ICS = inhaled corticosteroid; LABA = long-acting beta-agonist; HFA = hydrofluoroalkane; mcg = microgram; pMDI = pressurized metered-dose inhaler.

Source: Clinical study reports.[8]

Baseline Characteristics

Efficacy Trials

Table 9 provides a summary of key baseline characteristics for the ICS groups of the two efficacy trials (studies 301 and 30017). In both studies, the patients enrolled were predominantly female (58%), white (80%), and never smokers (86%). BMI values seemed to include patients who were between 12 and 17 years old. There was a mean baseline per cent predicted FEV_1 value of between 64% and 67% observed for patients in both studies.

Within Study 301, the mean age of patients was similar between groups (40.6 to 43.3 years), with the majority of patients between 18 and 64 years of age (72% to 78%). There was a higher proportion of patients in the 55 mcg Fp MDPI group who were 65 years of age or older (18%) compared with the placebo and 113 mcg Fp MDPI group (8% each). There was also a higher number of patients in the 55 mcg Fp MDPI group with a duration of asthma for one to five years (13%) in comparison with those taking placebo or 113 mcg Fp MDPI (8% to 9%). Within Study 30017, there was a higher proportion of patients who were black in the 113 mcg Fp MDPI group (21%) compared with the placebo (12%) and 232 mcg Fp MDPI (16%) groups. There was also a higher proportion of patients in the Fp MDPI 113 mcg group previously taking montelukast (6%) compared with the Fp MDPI 232 mcg group (3%) and placebo group (2%). Finally, there was a higher proportion of patients previously

taking montelukast in the Fp MDPI 113 mcg group (6%) compared with those in the placebo (2%) and those in the Fp MDPI 232 mcg group (3%).

When comparing the two studies, the mean age in the treatment group (44.3 to 45.7 years) was slightly higher in Study 30017 compared with Study 301 (40.6 to 43.3 years). There were also fewer patients between the ages of 12 and 17 in this study (4% to 8%), and a slightly higher proportion of patients in the 55 mcg Fp MDPI group of this study who were 65 years of age or older (18%). As expected by the study design, more patients in Study 30017 had previously been treated with ICS/LABA (50% to 60%) compared with ICS monotherapy (40% to 50%).

Table 8: Summary of Baseline Characteristics for Efficacy Trials

Baseline Characteristics		Study 301			Study 30017		
		Placebo (N = 130)	55 mcg b.i.d. (N = 129)	113 mcg b.i.d. (N = 130)	Placebo (N = 145)	113 mcg b.i.d. (N = 146)	232 mcg b.i.d. (N = 146)
Age (years)	Mean (SD)	40.9 (17.35)	43.3 (17.96)	40.6 (17.16)	44.5 (16.05)	45.7 (15.64)	44.4 (16.36)
	Median (range)	44.0 (12.0 to 78.0)	43.0 (12.0 to 79.0)	44.0 (12.0 to 75.0)	47.0 (13.0 to 76.0)	47.0 (12.0, 84.0)	46.0 (12.0 to 81.0)
	12 to 17 years, n (%)	17 (13)	13 (10)	18 (14)	6 (4)	9 (6)	10 (7)
	18 to 64 years, n (%)	102 (78)	93 (72)	102 (78)	125 (86)	124 (85)	119 (82)
	65+ years, n (%)	11 (8)	23 (18)	10 (8)	14 (10)	13 (9)	17 (12)
Sex, n (%)	Male	60 (46)	54 (42)	54 (42)	54 (37)	52 (36)	58 (40)
	Female	70 (54)	75 (58)	76 (58)	91 (63)	94 (64)	88 (60)
Race, n (%)	White	101 (78)	107 (83)	93 (72)	124 (86)	111 (76)	116 (79)
	African-American	26 (20)	18 (14)	30 (23)	18 (12)	31 (21)	23 (16)
	Asian	1 (< 1)	1 (< 1)	4 (3)	2 (1)	0	2 (1)
	American-Indian or Alaska Native	0	0	1 (< 1)	0	0	2 (1)
	Native Hawaiian or other Pacific Islander	0	1 (< 1)	0	0	0	0
	Other	2 (2)	2 (2)	2 (2)	1 (< 1)	4 (3)	3 (2)
Ethnicity, n (%)	Not Hispanic or Latino	122 (94)	121 (94)	114 (88)	136 (94)	134 (92)	136 (93)
	Hispanic or Latino	7 (5)	8 (6)	16 (12)	8 (6)	11 (8)	10 (7)
	Unknown	1 (< 1)	0	0	1 (< 1)	1 (< 1)	0
BMI (kg/m^2)	Mean (SD)	27.99 (6.849)	27.94 (7.259)	27.63 (6.603)	29.3 (7.41)	29.9 (7.62)	29.9 (7.27)
	Median (range)	27.0 (14.6 to 51.5)	27.0 (13.8 to 52.6)	27.0 (15.8 to 61.7)	27.9 (16.0 to 56.6)	28.6 (16.2 to 50.9)	29.0 (14.4 to 51.4)
Duration of asthma, n	3 to < 6 months	1 (< 1)	2 (2)	0	0	0	0

Baseline Characteristics		Study 301			Study 30017		
		Placebo (N = 130)	55 mcg b.i.d. (N = 129)	113 mcg b.i.d. (N = 130)	Placebo (N = 145)	113 mcg b.i.d. (N = 146)	232 mcg b.i.d. (N = 146)
(%)	6 months to < 1 year	2 (2)	0	1 (< 1)	4 (3)	1 (< 1)	0
	1 to < 5 years	12 (9)	17 (13)	11 (8)	13 (9)	16 (11)	11 (8)
	5 to < 10 years	32 (25)	26 (20)	24 (18)	23 (16)	15 (10)	36 (25)
	10 to < 15 years	22 (17)	18 (14)	27 (21)	22 (15)	25 (17)	13 (9)
	15 years or longer	61 (47)	66 (51)	67 (52)	83 (57)	88 (60)	86 (59)
History of smoking	Prior smoker	12 (9)	14 (11)	15 (12)	23 (16)	28 (19)	21 (14)
	No tobacco use	118 (91)	115 (89)	115 (88)	122 (84)	118 (81)	125 (86)
Number of pack-years	n	12	14	15	23	28	21
	Mean (SD)	3.7 (2.82)	2.4 (2.46)	4.6 (2.96)	4.1 (2.80)	3.5 (2.40)	4.8 (2.38)
	Median (range)	3.5 (0.5 to 9.0)	1.3 (0.5 to 9.5)	5.5 (0.8 to 9.5)	4.2 (0.1 to 9.5)	3.9 (0.1 to 8.2)	5.0 (1.0 to 9.5)
Previous therapy	ICS	102 (78)	89 (69)	83 (64)	68 (47)	58 (40)	63 (43)
	ICS/LABA	28 (22)	40 (31)	47 (36)	77 (53)	88 (60)	83 (57)
FEV_1 (L)	Mean (SD)	2.188 (0.5628)	2.132 (0.6341)	2.166 (0.5725)	2.141 (0.6849)	2.069 (0.6017)	2.075 (0.5696)
	Median (range)	2.095 (0.980 to 3.910)	2.025 (0.840 to 4.145)	2.100 (0.915 to 3.890)	1.975 (0.765 to 3.860)	1.980 (0.885 to 4.090)	2.020 (0.870 to 3.640)
FVC (L)	Mean (SD)	3.282 (0.9005)	3.211 (0.9732)	3.218 (0.9094)	3.210 (0.9745)	3.096 (0.9317)	3.186 (0.8939)
	Median (range)	3.110 (1.400 to 5.925)	3.040 (1.405 to 6.140)	2.975 (1.265 to 6.480)	3.040 (1.330 to 5.755)	2.840 (1.325 to 6.015)	3.043 (1.395 to 5.470)
FEF_{25-75} (L/sec)	Mean (SD)	1.464 (0.6337)	1.389 (0.5955)	1.515 (0.7693)	1.417 (0.7319)	1.395 (0.6844)	1.326 (0.6630)
	Median (range)	1.410 (0.380 to 3.240)	1.270 (0.290 to 3.360)	1.380 (0.475 to 4.070)	1.260 (0.355 to 4.135)	1.305 (0.235 to 4.180)	1.208 (0.290 to 3.720)
FEV_1/FVC (%)	Mean (SD)	67.611 (9.7695)	67.096 (9.000)	68.474 (11.1377)	67.090 (9.9384)	67.680 (10.4512)	66.008 (10.8542)
	Median (range)	67.550 (42.000 to 89.100)	67.150 (44.700 to 94.550)	69.150 (43.450 to 99.500)	67.025 (38.000 to 90.250)	67.450 (37.450 to 95.650)	65.425 (38.550 to 98.450)
Per cent of predicted FEV_1 (%)	Mean (SD)	66.96 (11.194)	66.47 (9.873)	67.09 (9.659)	65.55 (10.747)	66.10 (10.748)	63.98 (10.068)
	Median (range)	69.50 (41.00 to 83.50)	67.50 (45.00 to 84.00)	68.00 (47.50 to 85.50)	66.00 (41.50 to 84.50)	66.50 (40.50 to 85.00)	64.75 (40.50 to 85.50)
Concomitant asthma medication at screening,	Salbutamol	113 (87)	116 (90)	106 (82)	125 (86)	124 (85)	132 (90)
	Fluticasone propionate	48 (37)	41 (32)	48 (37)	53 (37)	66 (45)	54 (37)
	Beclo-metasone	31 (24)	35 (27)	25 (19)	12 (8)	12 (8)	14 (10)

Baseline Characteristics		Study 301			Study 30017		
		Placebo (N = 130)	55 mcg b.i.d. (N = 129)	113 mcg b.i.d. (N = 130)	Placebo (N = 145)	113 mcg b.i.d. (N = 146)	232 mcg b.i.d. (N = 146)
n (%)	dipropionate						
	Budesonide	28 (22)	33 (26)	29 (22)	44 (30)	43 (29)	44 (30)
	Fluticasone propionate and salmeterol xinafoate (Seretide)	19 (15)	23 (18)	26 (20)	37 (26)	48 (33)	41 (28)
	Salbutamol sulphate	15 (12)	12 (9)	17 (13)	17 (12)	16 (11)	9 (6)
	Budesonide with formoterol fumarate	10 (8)	10 (8)	14 (11)	23 (16)	22 (15)	31 (21)
	Mometasone furoate and formoterol fumarate (Dulera)	2 (2)	5 (4)	8 (6)	13 (9)	11 (8)	10 (7)
	Mometasone furoate	8 (6)	4 (3)	8 (6)	14 (10)	7 (5)	11 (8)
	Ciclesonide	4 (3)	5 (4)	9 (7)	15 (10)	8 (5)	7 (5)
	Montelukast	7 (5)	7 (5)	5 (4)	3 (2)	9 (6)	5 (3)

BMI = body mass index; FEF_{25-75} = forced expiratory flow at 25% to 75%; FEV_1 = forced expiratory volume in one second; FEV_1/ FVC= ratio of the forced expiratory volume in one second to the full forced vital capacity; Fp MDPI = fluticasone propionate multidose dry powder inhaler; FVC = force vital capacity; ICS = inhaled corticosteroid; n = number of patients with characteristic; N = total number of patients; SD = standard deviation.

Source: Clinical study report.[6,7]

Safety Trial

Table 9 provides a summary of key baseline characteristics for the ICS group of the safety trial (Study 305). The majority of patients in all treatment groups were between 18 and 64 years of age, with the Fp HFA 220 mcg group containing the largest proportion of these patients (85%) relative to the other groups (76%). The proportion of females was consistent across the groups ranging from 61% to 62%.

Between the medium-strength ICS categories, the 113 mcg Fp MDPI group had a lower proportion of prior smokers compared with the Fp HFA 110 mcg group (20% versus 24%), but the number of pack-years reported for the prior smokers was greater with the Fp MDPI 113 mcg group (4.0 years) compared with Fp HFA 110 mcg twice daily group (3.7 years). There was also a higher number of patients in the Fp MDPI 113 mcg category who were white (87%) compared with patients in the Fp HFA 110 mcg group (62%), and a lower number of black in the Fp MDPI 113 mcg group (13%) compared with the Fp HFA 110 mcg group (31%).

Within the medium-strength ICS cohort, 7% of patients in the Fp MDPI 113 mcg arm were concomitantly using montelukast, compared with 14% in the Fp HFA arm. Within the high-strength ICS cohort, 12% of patients in the Fp MDPI 232 mcg arm were taking montelukast, compared with 7% in the Fp HFA 220 mcg arm.

Between the high-strength ICS categories, the 232 mcg Fp MDPI group had a higher proportion of patients who were 12 to 17 years of age (13%) than patients in the Fp HFA 220 mcg group (7%). There was also a smaller proportion of patients who were between 18 to 64 years of age than patients in the Fp HFA 220 mcg group (85%). Regardless, the mean age of both groups appeared to be similar. With regard to race, there was a higher proportion of patients in the 232 mcg Fp MDPI group who were black (17%) compared with those in the Fp HFA 220 mcg arm (12%), and a lower percentage of patients in the Fp MDPI 232 mcg arm who were white (79%) compared with those in the Fp HFA 220 mcg arm (88%). Finally, the 232 mcg FP MDPI group had a greater proportion of prior smokers compared with the Fp HFA 220 mcg twice daily group (16% versus 12%) and a greater mean number of pack-years for those prior smokers (2.8 versus 1.9 years).

Table 9: Summary of Baseline Characteristics for Safety Trial

Baseline Characteristics		Medium-Strength ICS		High-Strength ICS	
		FP MDPI 113 mcg b.i.d. (N = 127)	Fp HFA 110 mcg b.i.d. (N = 42)	FP MDPI 232 mcg b.i.d. (N = 126)	Fp HFA 220 mcg b.i.d. (N = 41)
Age (years)	Mean (SD)	41.5 (17.93)	38.4 (18.10)	42.0 (17.28)	43.6 (16.74)
	Median	41.0	40.0	44.5	46.0
	12 to 17 Years	19 (15)	7 (17)	16 (13)	3 (7)
	18 to 64 Years	96 (76)	32 (76)	96 (76)	35 (85)
	65 + Years	12 (9)	3 (7)	12 (10)	3 (7)
	Not reported	0	0	2 (2)	0
Ethnicity, n (%)	Not Hispanic/Latino	118 (93)	39 (93)	100 (79)	33 (80)
	Hispanic/Latino	9 (7)	3 (7)	24 (19)	8 (20)
	Unknown	0	0	0	0
	Missing	0	0	2 (2)	0
Race, n (%)	White	110 (87)	26 (62)	99 (79)	36 (88)
	Black	16 (13)	13 (31)	22 (17)	5 (12)
	Asian	1 (< 1)	1 (2)	1 (< 1)	0
	American-Indian or Alaska Native	0	1 (2)	0	0
	Pacific Islander	0	0	2 (2)	0
	Other	0	1 (2)	0	0
	Not reported	0	0	2 (2)	0
Sex, n (%)	Male	49 (39)	16 (38)	46 (37)	16 (39)
	Female	78 (61)	26 (62)	78 (62)	25 (61)
	Not reported	0	0	2 (2)	0
Weight (kg)	Mean (SD)	80.7 (22.23)	87.6 (22.23)	83.4 (22.89)	83.7 (20.60)
	Median (range)	78.9 (37.5, 160.0)	82.2 (48.8, 140.6)	78.2 (44.1, 163.3)	82.1 (48.1, 152.9)
Height (cm)	Mean (SD)	167.6 (10.33)	170.4 (7.72)	167.2 (9.87)	166.3 (9.83)
	Median (range)	167.6 (152.4 to 194.2)	169.5 (149.9 to 185.4)	166.1 (147.3 to 195.6)	165.0 (149.0 to 190.5)
BMI (kg/m^2)	Mean (SD)	28.6 (7.54)	30.2 (7.77)	29.8 (7.63)	30.1 (5.95)
	Median (range)	27.1 (15.9, 56.0)	29.5 (17.9, 50.1)	28.7 (17.9, 59.9)	30.9 (19.4, 42.1)
FEV_1 (L)	Mean (SD)	2.54 (0.795)	2.70 (0.822)	2.56 (0.847)	2.43 (0.792)
	Median (range)	2.43	2.71	2.53	2.39

Baseline Characteristics		Medium-Strength ICS		High-Strength ICS	
		FP MDPI 113 mcg b.i.d. (N = 127)	Fp HFA 110 mcg b.i.d. (N = 42)	FP MDPI 232 mcg b.i.d. (N = 126)	Fp HFA 220 mcg b.i.d. (N = 41)
		(1.13, 4.78)	(1.25, 4.85)	(0.95, 5.59)	(1.06, 4.11)
FVC (L)	Mean (SD)	3.52 (1.007)	3.71 (1.172)	3.42 (1.069)	3.40 (1.030)
	Median (range)	3.48 (1.38, 6.48)	3.63 (1.92, 7.10)	3.32 (1.47, 7.42)	3.32 (1.56, 5.80)
FEF_{25-75} (L)	Mean (SD)	2.11 (1.071)	2.34 (1.232)	2.28 (1.266)	2.02 (1.073)
	Median (range)	1.89 (0.43, 6.96)	2.00 (0.86, 6.69)	2.08 (0.50, 8.73)	1.89 (0.43, 5.26)
History of smoking	Prior smoker	26 (20)	10 (24)	20 (16)	5 (12)
	No tobacco use	101 (80)	32 (76)	106 (84)	36 (88)
Number of pack-years	Mean (SD)	4.0 (2.53)	3.7 (2.93)	2.8 (2.72)	1.9 (1.69)
	Median (range)	5.0 (0.0, 9.0)	3.7 (0.3, 8.5)	2.2 (0.0, 9.5)	1.0 (0.2, 4.0)
Duration of Asthma	3 to <6 months	0	0	0	1 (2)
	6 months to < 1 year	2 (2)	0	1 (<1)	0
	1 to < 5 years	5 (4)	1 (2)	20 (16)	1 (2)
	5 to < 10 years	17 (13)	5 (12)	8 (7)	3 (7)
	10 to < 15 years	19 (15)	7 (17)	15 (12)	6 (15)
	15 years or longer	84 (66)	29 (69)	78 (62)	30 (73)
Concomitant asthma medication at screening, n (%)	Salbutamol	98 (77)	32 (76)	89 (71)	29 (71)
	Fluticasone propionate	55 (43)	23 (55)	52 (41)	22 (54)
	Beclomethasone dipropionate	14 (11)	2 (5)	32 (25)	7 (17)
	Budesonide	26 (20)	10 (24)	9 (7)	2 (5)
	Salbutamol sulphate	31 (24)	10 (24)	56 (44)	22 (54)
	Budesonide and formoterol fumarate	7 (6)	1 (2)	16 (13)	7 (17)
	Fluticasone propionate and salmeterol xinafoate (Seretide)	31 (24)	10 (24)	56 (44)	22 (54)
	Mometasone furoate and formoterol fumarate (Dulera)	11 (9)	4 (10)	13 (10)	3 (7)
	Mometasone furoate	13 (10)	5 (12)	7 (6)	4 (10)
	Ciclesonide	3 (2)	0	6 (5)	4 (10)
	Montelukast	9 (7)	6 (14)	15 (12)	3 (7)

BMI = body mass index; FEF_{25-75} = forced expiratory flow at 25% to 75%; FEV_1 = forced expiratory volume in one second; Fp MDPI = fluticasone propionate multidose dry powder inhaler; Fp HFA = fluticasone propionate hydrofluoroalkane; FVC = force vital capacity; ICS = inhaled corticosteroid; n = number of patients with characteristic; N = total number of patients; SD = standard deviation.

Source: Clinical study report.[8]

Interventions

Efficacy Trials (Studies 301 and 30017)

Table 10 provides a summary of treatments that were used in the studies 301 and 30017. All treatments were administered in a double-blind manner, and Fp MDPI was investigated at multiple dosages.

Table 10: Treatments Administered in Studies 301 and 30017

Study	Treatments	Daily Dosage	Blinding
Study 301	Fp MDPI 55 mcg b.i.d.	110 mcg	Double blind
	Fp MDPI 113 mcg b.i.d.	226 mcg	
	Placebo MDPI b.i.d.	NA	
Study 30017	Fp MDPI 113 mcg b.i.d.	226 mcg	Double blind
	Fp MDPI 232 mcg b.i.d.	464 mcg	
	Placebo MDPI b.i.d.	NA	

b.i.d. = twice daily; Fp MDPI= fluticasone propionate multidose dry powder inhaler; NA = not applicable.

Source: Clinical study reports.[6,7]

During the run-in period, all patients replaced their current rescue medication with study-specific rescue medication (albuterol/salbutamol HFA MDI) for use as needed. In addition, all patients discontinued their current ICS or ICS/LABA, and took either one inhalation twice daily of Fp MDPI 55 mcg twice daily (Study 30017) or from each of a single-blinded placebo MDPI device, and open-label beclomethasone dipropionate 40 mcg HFA pressurized MDI (or a clinically equivalent dose that was substituted in countries where beclomethasone dipropionate 40 mcg was unavailable) twice daily (Study 301). ICS, LABA, oral corticosteroids, and other medications were prohibited or restricted during the run-in period and throughout the duration of these studies, as outlined in Table 11.

Table 11: Prohibited Medications During Studies 301 and 30017

Type of Medication	Washout Period Before the Screening Visit (Unless Otherwise Specified)
Anti-immunoglobulin E therapy (omalizumab)	90 days
Any other investigational drug	30 days
Acetylsalicylic acid[a]	1 day
Beta-adrenergic receptor blocking drugs	30 days
Bisphosphonates (oral or intravenous)	30 days
Corticosteroids (oral, intravenous, intra-articular, intramuscular)[b]	30 days
Cromones	14 days
Decongestants (e.g., pseudoephedrine)	Discontinue 24 hours before SV, RV and TV, and resume use after the visit
Immunologically active biologic medications (e.g., antitumour necrosis factor alpha drugs)	90 days
Immunosuppressive therapy (e.g., methotrexate)	30 days
Immunotherapy[c]	Initiation within 90 days or change in dose within 90 days or change in dose within 30 days
Inhaled anticholinergic medication (e.g., tiotropium bromide)	7 days
Inhaled corticosteroids other than study drug	Permitted at SV, but discontinue upon entering run-in
Inhaled LABA	7 days

Type of Medication	Washout Period Before the Screening Visit (Unless Otherwise Specified)
Intranasal aerosol corticosteroids[d]	Discontinue at SV
Leukotriene modifiers	7 days
Monoamine oxidase inhibitors	14 days
Oral beta-2 agonists (tablets, syrup)	7 days
Oral or nasal antihistamines (e.g., loratadine, diphenhydramine, cetirizine)	Discontinue 24 hours before SV, RV, and nine of 10 TV and resume use after completion of the visit
Strong CYP3A4 inhibitors (ex. azole antifungals, ritonavir, clarithromycin)	30 days
Theophyllines	14 days
Topical dermatologic corticosteroids (intermediate to high potency)[e]	14 days
Marijuana (medical, legal, illegal)	30 days before the SV and throughout the study
Electronic cigarettes	Discontinue 24 hours before the SV and discontinue upon entering run-in
Tricyclic antidepressants	14 days

CYP = cytochrome P450; LABA = long-acting beta-agonists; RV = randomization visit; SV = screening visit; TV = treatment visits.

[a] Chronic stable doses of ASA (no more than 325 mg/day) for cardiovascular prophylaxis are allowed.

[b] Chronic stable doses of ocular steroids of at least 7 days duration, with doses expected to remain stable throughout the study, are allowed.

[c] Immunotherapy for the treatment of allergies by any route is permitted as long as therapy was initiated 90 days or more before the SV and the patient has been on a stable dose for 30 days or more before the SV. The patient must remain on this stable regimen throughout the study.

[d] Chronic stable doses of aqueous intranasal corticosteroids of at least 7 days' duration before the SV and stable throughout the study duration for the treatment of allergic rhinitis are allowed throughout the study.

[e] Chronic and as-needed doses of low potency topical corticosteroids (e.g.,1% hydrocortisone cream) covering < 20% of body surface area are allowed; no occlusive dressings are allowed.

Source: Clinical study reports.[6,7]

Patients in both studies were randomized to receive either Fp MDPI (Aermony RespiClick) or a placebo product, manufactured by Teva, which was supplied in a MDPI device identical to the devices used to deliver active drug, and indistinguishable from Fp MDPI. Patients in Study 301 were randomly assigned to receive either Fp MDPI 55 mcg twice daily, Fp MDPI 113 mcg twice daily or placebo twice daily for the duration of the treatment period, and patients in Study 30017 were randomly assigned to receive either Fp MDPI 113 mcg twice daily, Fp MDPI 232 mcg twice daily, or placebo twice daily for the duration of the treatment period.

Training on the MDPI device was provided at every visit from the point of screening (which was 14 to 21 days before randomization) to the penultimate treatment visit (week 10). Study adherence was checked during all visits beginning at the randomization visit, on the first day of double-blind study drug administration, up to the end of week 12, or until early termination. Adherence was recorded in each patient's dispensed daily diary and reviewed by the investigator or medically qualified designee. Treatment adherence during these studies was assessed based on data collected in the MDPI's dose counter and the patient's diary.

Safety Trial (Study 305)

Patients in this trial were randomized to receive either Fp MDPI (Aermony RespiClick) or Fp HFA (Flovent HFA), which is a pressurized metered-dose inhaler (MDI) that also administers fluticasone propionate. Fp HFA was not administered with the use of a spacer device. Patients were assigned to the ICS-monotherapy cohort (Figure 3) based on their baseline asthma maintenance therapy, and stratified into either medium- or high-treatment strength (Table 12). Patients in the medium-strength ICS treatment groups were

randomized to take either one inhalation of Fp MDPI 113 mcg twice daily or two inhalations of Fp HFA 110 mcg twice daily. Patients in the high-strength ICS treatment groups were randomized to take either one inhalation Fp MDPI 232 mcg twice daily or two inhalations of Fp HFA 220 mcg twice daily.

Table 12: Doses Used in Safety Study 305

Strength	Active Devices	Total Daily Dosage (mcg)	Blinding
Medium	Fp MDPI 113 mcg b.i.d.	226 mcg	Open-label
	Fp HFA 110 mcg b.i.d.	440 mcg	
High	Fp MDPI 232 mcg b.i.d.	464 mcg	Open-label
	Fp HFA 220 mcg b.i.d.	880 mcg	

b.i.d. = twice daily; Fp MDPI = fluticasone propionate multidose dry powder inhaler; Fp HFA = fluticasone propionate hydrofluoroalkane.

Source: Clinical study report.[8]

During the run-in period of this trial, patients were instructed to continue their current asthma medication, such as ICS or ICS/LABA. However, all patients replaced their current rescue medications (i.e.,. SABA) with albuterol or salbutamol HFA. Concomitant medication use was monitored and recorded throughout the study. The medications listed in Table 13 were to be discontinued for specified times leading up to the screening visit and prohibited for the length of the trial. This list of prohibited medications in this trial (Study 305) differed from studies 301 and 30017 in that ICS or LABA therapy were discontinued upon randomization and therefore allowed during the run-in period, and that leukotriene modifiers were permitted to be used.

Table 13: Prohibited Medications During Study 305

Type of Medication	Washout Period Before the Screening Visit (Unless Otherwise Specified)
Anti-immunoglobulin E therapy (omalizumab)	90 days
Any other investigational drug	30 days
Acetylsalicylic acid[a]	1 day
Beta-adrenergic receptor blocking drugs	30 days
Bisphosphonates (oral or intravenous)	30 days
Corticosteroids (oral, intravenous, intra-articular, intramuscular)[b]	30 days
Cromones	14 days
Decongestants (e.g., pseudoephedrine)	Discontinue 24 hours before SV, RV and TV, and resume use after the visit
Immunologically active biologic medications (e.g., antitumour necrosis factor alpha drugs)	90 days
Immunosuppressive therapy (e.g., methotrexate)	30 days
Immunotherapy[c]	Initiation within 90 days or change in dose within 90 days or change in dose within 30 days
Inhaled anticholinergic medication (e.g., tiotropium bromide)	7 days
Inhaled corticosteroids other than study drug	Discontinue upon randomization
Inhaled LABA other than study drug	Discontinue upon randomization
Intranasal aerosol corticosteroids[d]	Discontinue at SV
Monoamine oxidase inhibitors	14 days
Oral beta-2 agonists (tablets, syrup)	7 days
Oral or nasal antihistamines (ex loratadine, diphenhydramine, cetirizine)	Discontinue 24 hours before SV, RV, and nine of ten TV and resume use after completion of the visit

Type of Medication	Washout Period Before the Screening Visit (Unless Otherwise Specified)
Strong CYP3A4 inhibitors (ex. azole antifungals, ritonavir, clarithromycin)	30 days
Theophyllines	14 days
Topical dermatologic corticosteroids (intermediate to high potency)[e]	14 days
Marijuana (medical, legal, illegal)	30 days before the SV and throughout the study
Electronic cigarettes	Discontinue 24 hours before the SV and discontinue upon entering run-in
Tricyclic antidepressants	14 days

LABA = long-acting beta-agonists; RV = randomization visit; SV = screening visit; TV = treatment visits.

[a] Chronic stable doses of ASA (no more than 325 mg/day) for cardiovascular prophylaxis are allowed.

[b] Chronic stable doses of ocular steroids of at least 7 days duration, with doses expected to remain stable throughout the study, are allowed.

[c] Immunotherapy for the treatment of allergies by any route is permitted as long as therapy was initiated 90 days or more before the SV and the patient has been on a stable dose for 30 days or more before the SV. The patient must remain on this stable regimen throughout the study.

[d] Chronic stable doses of aqueous intranasal corticosteroids of at least 7 days' duration before the SV and stable throughout the study duration for the treatment of allergic rhinitis are allowed throughout the study.

[e] Chronic and as-needed doses of low potency topical corticosteroids (e.g.,1% hydrocortisone cream) covering < 20% of body surface area are allowed; no occlusive dressings are allowed.

Source: Clinical study report.[8]

Study drug training on the inhaler devices was provided at every visit from the randomization visit up until the penultimate treatment visit (week 22). Study adherence was checked during all visits beginning at the randomization visit, on the first day of the open-label study, up to the end of week 26, or early termination. Adherence was recorded in each patient's dispensed daily diary and reviewed by the investigator or medically qualified designee. Treatment adherence during these studies was assessed based on data collected in the device's dose counter and the patient's diary.

Outcomes

See Appendix 5 for detailed information on the outcomes used in the included studies.

Asthma Exacerbations

In the two efficacy trials, an exacerbation was defined as worsening asthma requiring any "significant treatment" other than study drug or rescue medication (salbutamol/albuterol HFA). Significant treatment included the use of systemic corticosteroids and/or urgent care or emergency department visit, or hospitalization. Urgent care or emergency department visits where the treatment was limited to a single dose of nebulized albuterol or salbutamol did not meet the criteria of significant treatment.

In the safety study, Study 305, a severe exacerbation was defined as an event requiring systemic corticosteroid use for ≥ 3 days, or hospitalization, or an emergency department visit because of asthma symptoms that required treatment with systemic corticosteroids. Time to first severe exacerbation was calculated from the date of first dose to the start date of the event. Patients who were lost to follow-up or who had not had not had a severe asthma exacerbation by week 26 were censored at the date of last assessment.

Exacerbations were secondary outcomes in the studies 301 and 30017.

Pulmonary Function

FEV_1 is the maximal volume of air after a full inspiration that can be forcibly exhaled in one second and is measured electronically by spirometry. However, although it is widely used in clinical trials to evaluate the effectiveness of asthma treatments, there is little literature on the MCID for FEV_1-based measures. Historically, an MCID of 0.100L has been proposed although little evidence exists to support this value. The minimum patient perceivable improvement value reported in the literature is a difference of 0.23 L.[31]

In the included studies, spirometry was performed at each study visit and was conducted within one hour of the time that the baseline spirometry measurement at the screening visit. At each visit at which spirometry was assessed, the highest FEV_1 value from three acceptable and two repeatable manoeuvres (maximum of eight attempts) was used. The average of the 30 and 10-minute predose FEV_1 measurements obtained at the randomization visit was the baseline for analysis of FEV_1 end points throughout the study. FEV_1 acceptability, reproducibility, and end of test consistent with American Thoracic Society/European Respiratory Society Task Force (ATS/ERS) criteria were required to be met.[25] All spirometry data were submitted to a blinded central reading centre for evaluation. Study participants were instructed to withhold their morning dose of asthma medication and were not to use any rescue medication for a minimum of six hours before the spirometry testing, or the test would be rescheduled.

Trough (pre-bronchodilator and predose) FEV_1 was calculated as the highest of three technically acceptable and two repeatable FEV_1 measurements before study medication and any rescue medication usage in studies 301 and 30017. In Study 305, it was only specified that the highest acceptable result of FEV_1 before the morning dose of study drug was recorded. The change from baseline in trough (morning predose and prerescue bronchodilator) FEV_1 at week 12 was the primary efficacy outcome for studies 301 and 30017, and was the principal efficacy outcome in safety Study 305.

Quality of Life

The Asthma Quality of Life Questionnaire for 18 years and older (AQLQ[S] 18+) with standardized activities is a variant of the standardized version of the Asthma Quality of Life Questionnaire (AQLQ). The questionnaire measures the impact of asthma on a patient's quality of life across four domains of activity limitations, symptoms, emotional function, and environmental stimuli and it includes 32 items with a two-week recall period. Each domain was scored on a 7-point Likert scale (7 = not impaired at all; 1 = severely impaired). The overall AQLQ(S) score is the mean of all 32 items, and the individual domain scores are the means of the items within each domain. The questionnaire was self-administered by patients 18 years and older only at the investigational centre at the randomization visit and the final treatment visit in studies 301 and 30017, before any other visit procedure was performed (AQLQ[S]18+ was not assessed in Study 305). The MCID has been estimated to be ≥ 0.5 points. Total scores were based on available data. Missing data at week 12 were imputed using last observation carried forward.

Patients between the ages of 12 and 17 at the time of enrolment assigned to complete the PAQLQ(S) (Pediatric Asthma Quality of Life Questionnaire With Standardized Activities). This questionnaire was also self-administered by patients only at the investigational centre at the randomization visit and final treatment visit before any other visit procedure was performed. The pediatric version of the questionnaire differed from the adult version in that

it consisted of 23 questions across three domains with a one-week recall period for activity limitations, symptoms, and emotional function.

Change from baseline in the mean AQLQ(S)18+ score was a secondary outcome in the efficacy studies. No health-related quality of life outcomes were measured in the safety trial, Study 305.

Total Daily Asthma Symptom Score

Symptom scores were to be recorded by patients in their diary, each morning and each evening, before taking any rescue or study medication, and before determining PEF. On the mornings of a scheduled treatment visit, symptom scores were completed before the visit. Symptom scores were assessed before spirometry or PEF measurements were obtained on study visit days. The change from baseline in the weekly average of the total daily asthma symptom score was assessed over weeks 1 to 12. The total daily asthma symptom score was the average of the daytime and nighttime scores.

Patients rated their daytime and nighttime symptoms according to a six-item or five-item Likert scale, respectively (Table 14).

Table 14: Daytime and Nighttime Asthma Symptom Score

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

Source: Clinical study reports.[6-8]

The total daily symptom score was considered missing if either the daytime or nighttime score was missing. The baseline was the average of recorded (nonmissing) scores over the seven days before randomization. The weekly average was based on scores recorded over the seven days before each analysis week.

Similarly, “symptom-free 24-hour period” related to the previous 24 hours in which patients did not have any asthma symptoms. The calculations of the percentage of symptom-free 24-hour periods at baseline was based on the seven days directly before the first study drug intake. To assess change from baseline, baseline was defined as the last seven consecutive days before randomization.

In studies 301 and 30017, changes in asthma symptom scores were a secondary outcome and changes in 24-hour symptom-free periods were an exploratory outcome. In Study 305, both changes in asthma symptoms score and symptom-free periods were exploratory outcomes.

No literature was identified that defines the MCID for the change from baseline in total daily asthma symptom score or symptom-free assessments.

Rescue Medication Use

Patients were permitted to take albuterol/salbutamol inhalation aerosol as rescue medication for as-needed relief of their asthma symptoms. Patients were to record the number of inhalations of rescue medications each morning and evening in the diary. The average number of daily inhalations over the seven days before the randomization visit was the baseline value. The weekly average was based on the available data for the seven days before each analysis week. A “rescue-free 24 hour period” related to the previous 24 hours in which patients did not require rescue medication. It was calculated as the total number of days during the treatment period minus the number of days during the treatment period with rescue medication usage. Missing rescue days were not included in the numerator or denominator for the per cent of rescue medication-free days summary. A minimum of 60% of full days during the 12-week treatment period could not be missing in order for a patient to be included in this analysis.

Changes in rescue medication use were secondary outcomes in the studies 301 and 30017, and an exploratory outcome in Study 305.

No literature was identified that defines the MCID for the change from baseline in the frequency of rescue medication use.

Asthma Control Test

The Asthma Control Test (ACT) is a patient-completed tool used for the assessment of overall asthma control. The questionnaire was to be completed by patients at the investigational centre. The five items included in the ACT assess daytime and nighttime asthma symptoms, use of rescue medication, and impact of asthma on daily functioning. Each item in the ACT is scored on a five-point scale with summation of all items providing scores ranging from 5 to 25. The highest score, 25, indicates complete control of asthma, and a lower score indicates more severe asthma symptoms. The MCID has been estimated in adults to be a difference of 3.09 (range: 1.06 to 5.28 points).

In the trials, the ACT total score was set to “missing” if all questions are not completed; otherwise the total score was calculated based on the available data.

Change from baseline in the mean ACT total score was an exploratory outcome in all three included studies.

Adherence

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

Health Care Resource Utilization

Health care resource utilization was assessed in the long-term safety study, Study 305. The number and percentages of patients with unscheduled office or outpatient visits, emergency department or urgent care facility usage, and those hospitalized during the 26-week treatment period were recorded by treatment group in this study.

Other Outcomes

Other outcomes pre-specified as being of interest for this review, days of missed work and/or school and ease of use of the interventions, were not reported in the included studies.

Harms

Study 305 was a safety study with a primary objective to evaluate the long-term safety of Fp MDPI during a period of 26 weeks. The primary outcome measure of this study was the incidence and type of all adverse events (AEs) for Fp MDPI.

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

Statistical Analysis

Determination of Sample Size

Sample size and power were calculated to demonstrate superiority of Fp MDPI 55 mcg twice daily compared with placebo in change from baseline in trough FEV_1 at week 12 in Study 301, and superiority of Fp MDPI 113 mcg twice daily compared with placebo in change from baseline in trough FEV_1 at week 12 in Study 30017. Safety was the primary objective of Study 305, and the determination of sample size for the safety analysis was not based on statistical considerations.

Study 301 had a power of 85% for a superiority comparison of Fp MDPI 55 mcg twice daily versus placebo with a difference of 0.130 L change from baseline in trough FEV_1 at week 12, assuming that 106 patients per treatment group (a total of 530 patients) remained by the end of week 12. Assuming a dropout rate of 15%, 125 patients per treatment group (a total of 625 patients) would yield a statistical power of at least 85%, at a significance level of 0.05 for demonstrating the superiority of Fp 55 mcg twice daily as compared with placebo.

Study 30017 had a power of 85% for a superiority comparison of Fp MDPI 113 mcg twice daily versus placebo with a difference of 0.130 L change from baseline in trough FEV_1 at week 12, assuming that 121 patients per treatment group (a total of 605 patients) remained by the end of week 12. Assuming a dropout rate of 15%, 143 patients per treatment group (a total of 715 patients) would yield a statistical power of at least 85%, at a significance level of 0.05 for demonstrating the superiority of Fp 55 mcg twice daily compared with placebo.

For the noninferiority assessment of change from baseline in trough FEV_1 during the 26-week treatment period in Study 305, the medium and high-strength data were combined and analyzed using a mixed model for repeated measures (MMRM) with fixed effects of treatment, time, and treatment-by-time interaction. A noninferiority margin was pre-specified as –0.125L, and 240 patients in the FS MDPI or Fp MDPI group as well as 80 patients in the comparator product group were expected to yield an approximate statistical power of 90% at a significance level of 0.025, for the one-sided noninferiority comparison.

The treatment effect and variability assumptions for power calculations in studies 301 and 30017 were based on data collected in Teva studies. The treatment effect and variability assumptions in Study 305 were based on results from a previous phase trial, Study 201.[17]

In the safety, open-label Study 305, no adjustments were made for multiple comparisons.

Statistical Test

Across the efficacy studies 301 and 30017, statistical testing was conducted according to the nature of the outcomes measure with a hypothesis driven by a two-sided analysis at a 0.05 significance level. All efficacy analyses were adjusted for baseline scores. In the safety study, 305, statistical testing was conducted according to the primary outcome, change from baseline in trough FEV_1, based on a hypothesis of noninferiority with a margin pre-specified as –0.125 L. This hypothesis was based on the pooled dosage arms of Fp MDPI and Fp HFA at a 0.025 one-sided significance level.

Efficacy Trials

Primary Efficacy Analysis: Change from baseline in trough FEV_1 at week 12 was the primary outcome for studies 301 and 30017. The analysis was performed using an ANCOVA model that included baseline trough FEV_1, sex, age, (pooled) centre, previous therapy (ICS or ICS/LABA), and treatment as covariates.

Secondary Efficacy Analyses: If all inferential comparisons in the primary analysis were significant (Table 15), then inferential testing was extended to the secondary analysis in a sequential manner, in accordance with a fixed-sequence multiple testing procedure (Table 16).

Weekly average of total daily asthma symptom scores: change from baseline in the weekly average of total daily asthma symptoms scores over weeks 1 to 12 in studies 301 and 30017, and over weeks one to 26 in Study 305. This outcome was analyzed using an MMRM with effects due to baseline score, sex, age, (pooled) centre, previous therapy (ICS or ICS/LABA), week, treatment, and week-by-treatment interaction.

Salbutamol/albuterol daily use: the change from baseline in the weekly average of total daily (24-hour) use of salbutamol/albuterol inhalation aerosol (number of inhalations) over weeks 1 to 12 was analyzed using an MMRM with an unstructured covariance matrix that included baseline value, sex, age, (pooled) centre, previous therapy (ICS or ICS/LABA), week, treatment, and week-by-treatment interaction as covariates. In Study 305, the number and percentage of weekly averages for total daily (24-hour) use of albuterol/salbutamol during the 26-week treatment period were recorded and summarized as continuous variables.

Patients withdrawn for worsening asthma (including acute exacerbations): the proportion of patients withdrawn for worsening asthma during the 12-week treatment period was analyzed over weeks 1 to 12 in studies 301 and 30017 using a logistic regression model

that included sex, age, (pooled) centre, previous therapy (ICS or ICS/LABA), and treatment as covariates.

Time to first severe asthma exacerbation was an outcome in Study 305, and calculated from the date of first dose to the start date of the event. The analysis of time to first severe asthma exacerbation criteria during the 26-week treatment period was performed using the Kaplan-Meier method. The log-rank test was used to compare the survival curves. Median time to first severe asthma exacerbation and associated 95% CIs were estimated as appropriate.

AQLQ(18+): In studies 301 and 30017, the change from baseline in AQLQ(S) score in patients ≥ 18 years of age was analyzed using an ANCOVA model with baseline AQLQ(S) score, sex, age, (pooled) centre, previous therapy (ICS or ICS/LABA), and treatment as covariates. The change from baseline in AQLQ(S) score in patients ≥ 18 years at last post-baseline observation was analyzed using an ANCOVA model with effects due to baseline AQLQ(S) score, sex, age, (pooled) centre, previous therapy (ICS or ICS/LABA), and treatment, imputing missing data through last observation carried forward (LOCF). In the statistical analysis plan for these trials, a combined single end point of AQLQ(S) and PAQLQ(S) was outlined. The protocol was subsequently amended due to the different numbers of questions and domains present within the two scores. As a result, only descriptive statistics were used to summarize results for PAQLQ(S) for patients 12 to 17 years old at week 12, as the number of adolescents expected to be enrolled into the trials was low.

Rescue-free/symptom-free 24-hour periods: In studies 301 and 30017, the change from baseline in the percentage of 24-hour periods with no use of rescue medication as well as the percentage of symptom-free 24-hour periods as recorded in patient diaries during the 12-week treatment period was compared between treatment groups using the Wilcoxon-Mann-Whitney test. In the safety Study 305, the number and percentage of rescue-free and symptom-free days during the 26-week treatment period were recorded and summarized as continuous variables.

Asthma-control 24-hour periods: in studies 301 and 30017, the change from baseline in the percentage of asthma-control 24-hour periods (defined as 24-hour periods with asthma symptom scores of zero and no rescue medication use) during the 12-week treatment period was summarized and compared between treatment groups using the Wilcoxon-Mann-Whitney test.

Multiple Comparisons

The co-primary end points in the efficacy trials were tested using a statistical testing hierarchy involving eight sequences to control the overall type I error rate at the 0.05 level (two-sided). (Note: based on input from the clinical expert consulted by CADTH the review focused on trough FEV_1 as most clinically relevant for the assessment of the effects of Fp.) In both studies 301 and 30017, the testing sequence began with four tests involving FEV_1 $AUEC_{0\text{-}12h}$ at 12 weeks followed by four tests involving trough FEV_1 at 12 weeks. As shown in Table 15, the testing hierarchy in both studies began with a comparison between the FS MDPI (ICS/LABA) formulations and the Fp MDPI (ICS) formulations for FEV_1 $AUEC_{0\text{-}12h}$ at 12 weeks, followed by comparisons between the FS MDPI formulations and placebo for FEV_1 $AUEC_{0\text{-}12h}$ at 12 weeks. Testing Fp MDPI versus placebo was not part of the statistical testing hierarchy for the FEV_1 $AUEC_{0\text{-}12h.}$ For trough FEV_1, each of the active treatment

groups were tested against placebo in descending order of the strength of the regimen (i.e., highest dose ICS/LABA was tested first and lowest dose ICS was tested last).

Table 15: Statistical Testing Hierarchy for Primary End Points in Efficacy Trials

Study	End Point	Comparison	Sequence
301	FEV_1 $AUEC_{0\text{-}12h}$ at 12 weeks[a]	FS MDPI 113 mcg/12.5 mcg b.i.d. versus Fp MDPI 113 mcg b.i.d.	1
		FS MDPI 55 mcg/12.5 mcg b.i.d. versus Fp MDPI 55 mcg b.i.d.	2
		FS MDPI 113 mcg/12.5 mcg b.i.d. versus placebo	3
		FS MDPI 55 mcg/12.5 mcg b.i.d. versus placebo	4
	Trough FEV_1 at 12 weeks	FS MDPI 113 mcg/12.5 mcg b.i.d. versus placebo	5
		FS MDPI 55 mcg/12.5 mcg b.i.d. versus placebo	6
		Fp MDPI 113 mcg b.i.d. versus placebo	7
		Fp MDPI 55 mcg b.i.d. versus placebo	8
30017	FEV_1 $AUEC_{0\text{-}12h}$ at 12 weeks[a]	FS MDPI 232 mcg/12.5 mcg b.i.d. versus Fp MDPI 232 mcg b.i.d.	1
		FS MDPI 113 mcg/12.5 mcg b.i.d. versus Fp MDPI 113 mcg b.i.d.	2
		FS MDPI 232 mcg/12.5 mcg b.i.d. versus placebo	3
		FS MDPI 113 mcg/12.5 mcg b.i.d. versus placebo	4
	Trough FEV_1 at 12 weeks	FS MDPI 232 mcg/12.5 mcg b.i.d. versus placebo	5
		FS MDPI 113 mcg/12.5 mcg b.i.d. versus placebo	6
		Fp MDPI 232 mcg b.i.d. versus placebo	7
		Fp MDPI 113 mcg b.i.d. versus placebo	8

b.i.d. = twice daily; FEV_1 = forced expiratory volume in one second; FEV_1 $AUEC_{0\text{-}12h}$ = standardized baseline-adjusted area under the effect curve for forced expiratory volume in one second from time 0 to 12 hours post-dose; Fp MDPI = fluticasone propionate multidose dry powder inhaler mcg = microgram.

[a] Based on input from clinical expert consulted by CADTH, this was not considered a relevant outcome for review.

Source: Clinical study reports.[6,7]

According to the statistical analysis plan for studies 301 and 30017, if all primary comparisons were statistically significant at the $P < 0.05$ level, an inferential testing procedure would subsequently be performed for the secondary efficacy end points for Fp MDPI at dosage strengths used in their respective study (Table 16).[32] This process was to continue testing sequentially through the each Fp MDPI strength for each variable in the order presented, until either all comparisons of interest were made, or until the point at which the resulting *P* value for a comparison was greater than 0.05. If a *P* value was found to be greater than 0.05, no further comparisons of either that strength or end point could be made. This procedure allowed for control of a type I error within each end point (or row), or each dose comparison over placebo (or column); however, it did not control the overall type I error.

Table 16: Statistical Testing Hierarchy for Secondary End Points in Efficacy Trials

Secondary End Point	Hypothesis Testing[a]			
	Study 301		Study 30017	
	Fp MDPI 113 mcg vs. Placebo	Fp MDPI 55 mcg vs. Placebo	Fp MDPI 232 mcg vs. Placebo	Fp MDPI 113 mcg vs. Placebo
Change from baseline in weekly average of daily trough morning PEF over the 12-week treatment period	↓→	↓	↓→	↓
Change from baseline in the weekly average of the total daily asthma symptom score over weeks 1 to 12	↓→	↓	↓→	↓
Change from baseline in the weekly average of total daily (24 hour) use of albuterol/salbutamol inhalation aerosol (number of inhalations) over weeks 1 to 12	↓→	↓	↓→	↓
Time to patient withdrawal for worsening asthma during the 12-week treatment period	↓→	↓	↓→	↓
Change from baseline in the AQLQ(S) score at end point	→	↓	→	↓

AQLQ(S) = Asthma Quality of Life Questionnaire With Standardized Activities; Fp MDPI = fluticasone propionate multidose dry powder inhaler; mcg = microgram; PEF = pulmonary expiratory flow; vs. = versus.

[a] Arrows indicate the direction of the sequence in which comparisons were made to placebo. This process tested sequentially through the next Fp MDPI strength until either all comparisons were made, or until the point at which the resulting *P* value for a comparison exceeded 0.05. At the point where the *P* value was greater than 0.05, no further comparisons of either that strength or measure could be made. FS MDPI comparisons were tested separately.

Source: Clinical study reports statistical analysis plan for studies 301 and 30017.[32]

All primary end point comparisons specified in the fixed-sequence multiple testing procedure were found to be statistically significant in studies 301 and 30017; therefore, inferential testing was extended to the secondary efficacy end points in a sequential manner until a comparison was reached that had a *P* value ≥ 0.05 (Table 16). The comparison for the first secondary end point in the hierarchy, change from baseline in the weekly average of the daily trough morning PEF, did not meet the $P < 0.05$ threshold for the comparison of Fp 55 mcg versus placebo in Study 301; hence, subsequent statistical comparisons were considered hypothesis generating. None of the secondary statistical comparisons in the hierarchy for Study 30017 failed to meet the pre-specified threshold for statistical significance.

In the safety, open-label Study 305, no adjustments were made for multiple comparisons.

Analysis Populations

The analysis populations that were used in the included studies are summarized in Table 17. The two efficacy trials used a full analysis set (FAS) for evaluating the efficacy end points, with intention to treat (ITT) and per-protocol (PP) datasets conducted as supportive analyses.

Table 17: Analysis Populations From the Included Studies

Analysis set	Description
Efficacy Trials (Studies 301 and 30017)	
ITT population	Included all randomized patients and was used in supportive efficacy analyses.
FAS population	Included all patients in the ITT population who received at least one dose of the post-randomization study treatments and had at least one post-baseline trough FEV_1 assessment. The FAS was used for the primary analyses of the efficacy end points.
PP population	Included all data from randomized patients prior to experiencing a major protocol violation and who had demonstrated 80% adherence with the study treatments over the entire treatment period. The PP population was used in supportive analyses for the primary efficacy analysis.
Safety population	Included all randomized patients who received at least one dose of study drug and was used for all analyses of safety data.
Serial spirometry subset[a]	Patients who were enrolled at one of the investigational centres that were preselected to conduct the serial spirometry evaluations. Patients could not opt out of serial spirometry participation. This population was used for the analysis of FEV_1 AUEC0-12h, a co-primary end point of studies 301 and 30017.
Safety Trial (Study 305)	
Safety population	Included all randomized patients who received at least one dose of the randomized study treatment. The safety population was used for all analyses of safety data.
ITT population	Included all randomized patients.
FAS population	Included all patients in the ITT population who received at least one dose of the study treatments and had at least one post-baseline trough FEV_1 assessment. The FAS was used for all analyses of efficacy data.

FAS = full analysis set; FEV_1 = force expiratory volume in one second; FEV_1 AUC0-12h = forced expiratory volume in 1 second from time 0 to 12 hours post-dose; ITT = intention to treat; PP = per-protocol.

[a] This subpopulation was not considered for this review.

Source: Clinical study reports.[6-8]

Missing Data

Analyses in Efficacy Trials

For the primary end point of change from baseline in trough FEV_1 at week 12, missing data caused by early dropout from study were handled by penalizing the positive change from baseline in trough FEV_1 score using a baseline-observation carried forward (BOCF) method. This method imputed data for those patients who had a change from baseline in trough FEV_1 score of zero, thus the discontinued patients would be treated as failures and assigned a poor score. Discontinued patients who had a negative change from baseline with last nonmissing FEV_1 score did not have their results adjusted. No adjustments were made to results for patients who had completed the study. For the MMRM, there was no imputation for missing data.

For secondary outcomes using the ANCOVA model, missing data were imputed through LOCF. Should either a morning or evening diary entry data be missing, but the other value was equal to zero, the available value was weighted by half, and the denominator was altered to reflect the missing value. If both morning and evening values were missing for a particular day, the value was not used in percentage calculations.

At the randomization visit measurement, patients were required to perform spirometry 30 minutes and 10 minutes before their morning dose of study drug. The baseline FEV_1 for this study was the average of the two predose FEV_1 measurements (30 and 10 minutes predose) at the randomization visit. If one predose FEV_1 measurement was missing, the other nonmissing measurement was used as baseline. If both predose FEV_1 measurements were missing, baseline was treated as missing.

Analyses in Safety Trial

In Study 305, only observed data from patients were used in the statistical analysis. Therefore, no imputation was employed for analysis using the MMRM. Missing diary entry data were treated similarly to the efficacy studies 301 and 30017. In the case that either a morning or evening diary entry was missing, but the other value was equal to zero, the available value was weighted by half, and the denominator was altered to reflect the missing value. If both morning and evening values were missing for a particular day, the value was not used in percentage calculations.

Sensitivity Analysis

Sensitivity analyses were conducted for the outcome of change from baseline in trough FEV_1 in the efficacy trials (studies 301 and 30017) and were performed using the ITT population. There was no multiplicity adjustment made for the supportive analyses of the primary end points.

Change from baseline in trough FEV_1 over the 12-week treatment period was analyzed using an MMRM with effects due to baseline FEV_1, sex, age, (pooled) centre, previous therapy (ICS or ICS/LABA), visit, treatment, and visit-by-treatment interaction. For this outcome, missing data were not implicitly imputed in the MMRM analysis, but all nonmissing data for a patient were used within the analysis to estimate the time-averaged difference between treatment groups over 12 weeks. Change from baseline in trough FEV_1 after the 12-week treatment period using MMRM was also an analysis as described for change over the 12-week period.

Change from baseline in FEV_1 after the 12-week treatment period was also analyzed using an ANCOVA including baseline FEV_1, sex, age, (pooled) centre, previous therapy (ICS or ICS/LABA), and treatment as covariates, imputing missing data using LOCF.

A tipping point analysis was performed to assess the robustness of study results in light of missing data. The analysis was performed for all comparisons of active drugs with placebo. This was employed to evaluate several combinations of imputed missing data, using multiple imputations under the missing not-at-random assumption. For the missing FEV_1 values for patients who discontinued treatment before week 12, values were imputed using this method. In the placebo group, the missing FEV_1 values were imputed based on measurements observed at previous visits and treatment groups, and were assumed to be missing at random. For the active treatment groups, missing FEV_1 values were imputed in the same manner, but a constant (positive value) shift was subtracted from the imputed FEV_1 values. The initial shift value was zero (representing missing at random) and was subsequently increased and the process repeated until the treatment effect would become no longer significant at the 5% level. The tipping point was defined as the shift point at which the effect was no longer significant.

Patient Disposition

Efficacy Trials

Table 18 provides a summary of the patient disposition from the ICS cohorts and placebo groups of the efficacy trials, studies 301 and 30017.

In Study 301, a total of 1,363 patients with persistent asthma were screened for enrolment. Of those screened, 787 patients at 129 investigational centres were considered eligible based on entry criteria. Of the 787 patients enrolled, 140 were not randomized. For 70

(50%) of these patients enrolled but not randomized, it was due to randomization criteria not being met, and for 30 (21%) of these patients, it was due to inclusion criteria not being met. The total ITT population included 647 patients, and the full analysis set (FAS) included 640 patients.

In Study 30017, a total of 1,661 patients with persistent asthma were screened for enrolment. Of those screened, 882 patients at 147 investigation centres were considered eligible for enrolment based on entry criteria. Of the 882 patients enrolled, 154 were not randomized. For 76 (49%) of these patients, it was also due to randomization criteria not being met, and for 25 (10%) of these patients, it was due to inclusion criteria not being met. The total ITT population included 728 patients, and the FAS included 720 patients.

Study completion was not consistent across treatment arms within each study. In Study 301, a lower proportion of patients randomized to the placebo group completed the study (87%) versus those in the Fp MDPI 55 mcg (94%) and Fp MDPI 113 mcg (93%) groups. Higher imbalances were observed in Study 30017, where 74% of patients in the placebo group completed the study, compared with 93% in the Fp MDPI 113 mcg group, and 92% in the Fp MDPI 232 mcg group. The most common reasons for discontinuation among patients in both studies were cited as disease progression, lack of efficacy, and AEs (including asthma-related AEs).

Table 18: Patient Disposition in the Efficacy Trials

Analysis Group n (%)	Study 301			Study 30017		
	Placebo	Fp MDPI 55 mcg b.i.d.	Fp MDPI 113 mcg b.i.d.	Placebo	Fp MDPI 113 mcg b.i.d.	Fp MDPI 232 mcg b.i.d.
Screened	1,363			1,661		
Randomized	130 (100)	129 (100)	130 (100)	145 (100)	146 (100)	146 (100)
Not treated	1 (< 1)	0	1 (< 1)	1 (< 1)	1 (< 1)	0
ITT population	130 (100)	129 (100)	130 (100)	145 (100)	146 (100)	146 (100)
Safety population	129 (> 99)	129 (100)	129 (> 99)	144 (> 99)	145 (> 99)	146 (100)
Full analysis set	129 (> 99)	128 (> 99)	129 (> 99)	143 (99)	145 (> 99)	146 (100)
PP population	128 (98)	125 (97)	125 (96)	140 (97)	142 (97)	144 (99)
Completed study	113 (87)	121 (94)	121 (93)	107 (74)	136 (93)	135 (92)
Discontinued	17 (13)	8 (6)	9 (7)	38 (26)	10 (7)	11 (8)
Death	0	0	0	0	0	0
Adverse event	6 (5)	1 (< 1)	2 (2)	2 (1)	2 (1)	0
Withdrawal by patient	2 (2)	3 (2)	2 (2)	7 (5)	4 (3)	3 (2)
Nonadherence	0	0	1 (< 1)	0	0	1 (< 1)
Protocol violation	1 (< 1)	1 (< 1)	1 (< 1)	1 (<1)	2 (1)	2 (1)
Disease progression	2 (2)	1 (< 1)	1 (< 1)	18 (12)	0	3 (2)
Pregnancy	0	0	0	0	0	0
Lost to follow-up	1 (< 1)	1 (< 1)	1 (< 1)	1 (<1)	0	1 (< 1)
Lack of efficacy	4 (3)	1 (< 1)	0	7 (5)	1 (< 1)	1 (<1)
Other	1 (< 1)	0	1 (< 1)	2 (1)	1 (< 1)	0

b.i.d. = twice daily; Fp MDPI = fluticasone propionate multidose dry powder inhaler; ITT = intention to treat; PP = per-protocol.

Source: Clinical study reports.[6,7]

Safety Trial

Table 19 provides a summary of the patient disposition from the ICS cohorts of the safety study. For both the medium-strength and high-strength comparisons, the proportion of patients who discontinued the studies was greater in the Fp HFA groups compared with the Fp MDPI groups (17% versus 13% and 12% versus 10%, respectively). Withdrawal by patient was the most commonly cited reason for all of the groups (range: 5% to 7%).

Table 19: Patient Disposition in Safety Trial

Disposition, n (%)	Medium-Strength		High-Strength	
	FP MDPI 113 mcg b.i.d. (N = 127)	Fp HFA 110 mcg b.i.d. (N = 42)	FP MDPI 232 mcg b.i.d. (N = 126)	Fp HFA 220 mcg b.i.d. (N = 41)
Randomized	127 (100)	42 (100)	126 (100)	41 (100)
Not treated	0	0	1 (< 1)	0
ITT population	127 (100)	42 (100)	126 (100)	41 (100)
Safety population	127 (100)	42 (100)	125 (> 99)	41 (100)
Full analysis set	123 (97)	42 (100)	120 (95)	41 (100)
Completed	111 (87)	35 (83)	113 (90)	36 (88)
Discontinued	16 (13)	7 (17)	13 (10)	5 (12)
Death	0	0	0	0
Adverse event	2 (2)	1 (2)	1 (< 1)	1 (2)
Withdrawal by patient	9 (7)	3 (7)	6 (5)	2 (5)
Nonadherence	1 (< 1)	2 (5)	0	0
Protocol violation	0	0	0	0
Disease progression	0	0	0	0
Pregnancy	0	0	0	0
Lost to follow-up	3 (2)	1 (2)	3 (2)	1 (2)
Lack of efficacy	0	0	0	0
Other	1 (< 1)	0	3 (2)	1 (2)

b.i.d. = twice daily; Fp HFA= fluticasone propionate hydrofluoroalkane; Fp MDPI = fluticasone propionate multidose dry powder inhaler; ITT = intention to treat; n = number of events.

Source: Clinical study reports.[8]

Exposure to Study Treatments

Table 20 and Table 21 provide a summary of exposure and adherence to the study treatments in the efficacy and safety trial, respectively.

In both efficacy trials, the majority of patients had between eight and 12 weeks of exposure to the study treatments. Consistent with the proportion of patients who discontinued from the studies, exposure to the study treatments was lower in the two placebo groups compared with the active groups. Adherence with the study treatments was at least 80% with the majority of patients in both the placebo- and active-control groups.

Table 20: Exposure to Study Treatments in the Efficacy Trials

Exposure and Adherence	Study 301			Study 30017		
	Placebo (N = 129)	Fp MDPI 55 mcg b.i.d. (N = 129)	Fp MDPI 113 mcg b.i.d. (N = 129)	Placebo (N = 144)	Fp MDPI 113 mcg b.i.d. (N = 145)	Fp MDPI 232 mcg b.i.d. (N = 146)

Exposure and Adherence		Study 301			Study 30017		
		Placebo (N = 129)	Fp MDPI 55 mcg b.i.d. (N = 129)	Fp MDPI 113 mcg b.i.d. (N = 129)	Placebo (N = 144)	Fp MDPI 113 mcg b.i.d. (N = 145)	Fp MDPI 232 mcg b.i.d. (N = 146)
Exposure	Mean days (SD)	79.6 (17.07)	82.0 (13.22)	82.1 (11.80)	70.5 (26.45)	81.3 (15.10)	81.5 (12.68)
	≤ 2 weeks	2 (2)	2 (2)	2 (2)	13 (9)	5 (3)	2 (1)
	>2 to ≤ 4 weeks	5 (4)	3 (2)	1 (<1)	11 (8)	2 (1)	2 (1)
	> 4 to ≤ 8 weeks	7 (5)	0	4 (3)	11 (8)	1 (< 1)	5 (3)
	> 8 to ≤ 12 weeks	112 (87)	122 (95)	120 (93)	108 (75)	137 (94)	135 (92)
	> 12 weeks	3 (2)	2 (2)	2 (2)	1 (< 1)	0	2 (1)
Diary adherence n (%)	≥ 100%	93 (72)	102 (79)	95 (74)	114 (79)	107 (74)	111 (76)
	80% to < 100%	35 (27)	27 (21)	33 (26)	29 (20)	38 (26)	35 (24)
	60% to < 80%	1 (< 1)	0	0	1 (< 1)	0	0
	< 60%	0	0	1 (< 1)	0	0	0
Device adherence n (%)	≥ 100%	56 (43)	73 (57)	56 (43)	62 (43)	69 (48)	75 (51)
	80% to < 100%	69 (53)	49 (38)	67 (52)	73 (51)	71 (49)	61 (42)
	60% to < 80%	3 (2)	5 (4)	1 (< 1)	3 (2)	1 (< 1)	5 (3)
	< 60%	0	0	1 (< 1)	0	0	1 (< 1)
	Missing	1 (<1)	2 (2)	4 (3)	6 (4)	4 (3)	4 (3)

b.i.d. = twice daily; Fp MDPI= fluticasone propionate multidose dry powder inhaler; n = number of events; SD = standard deviation.

Source: Clinical study reports.[6,7]

In the safety Study 305, mean duration of exposure was similar in the two medium-strength ICS groups (169 days with Fp MDPI 100 mcg twice daily and 166 days with Fp HFA 110 mcg twice daily) and the two high-strength ICS cohorts (170 days with Fp MDPI 232 mcg twice daily and 171 days with Fp HFA 220 mcg twice daily). The majority of patients in all four ICS groups received between 22 and 26 weeks of treatment (range: 84% to 88%). The proportion of patients who reported 100% adherence with the study treatments was greater in the two Fp HFA groups (93% with 110 mcg and 98% with 220 mcg) compared with the Fp MDPI groups (range: 30% to 42%).

Table 21: Exposure to Study Treatments in the Safety Trial

Exposure and Adherence		Medium Strength		High Strength	
		AR 113 mcg b.i.d. (N = 127)	Fp HFA 110 mcg b.i.d. (N = 42)	FP MDPI 232 mcg b.i.d. (N = 125)	Fp HFA 220 mcg b.i.d. (N = 41)
Exposure	Mean days (SD)	169 (41.2)	166 (43.8)	170 (40.3)	171 (35.6)
	≤ 2 weeks	5 (4)	0	6 (5)	1 (2)
	> 2 to ≤ 6 weeks	1 (<1)	4 (10)	0	0
	> 6 to ≤ 10 weeks	3 (2)	1 (2)	2 (2)	1 (2)
	> 10 to ≤ 14 weeks	3 (2)	0	1 (< 1)	1 (2)
	> 14 to ≤ 18 weeks	3 (2)	0	2 (2)	1 (2)
	> 18 to ≤ 22 weeks	0	1 (2)	2 (2)	1 (2)
	> 22 to ≤ 26 weeks	107 (84)	36 (86)	110 (88)	35 (85)
	> 26 weeks	5 (4)	0	2 (2)	1 (2)
Diary adherence n (%)	≥ 100%	36 (28)	16 (38)	51 (41)	13 (32)
	80% to < 100%	86 (68)	24 (57)	67 (54)	28 (68)
	60% to < 80%	2 (2)	1 (2)	3 (2)	0
	< 60%	3 (2)	1 (2)	3 (2)	0
	Missing	0	0	1 (<1)	0
Device adherence n (%)	≥ 100%	38 (30)	39 (93)	52 (42)	40 (98)
	80% to < 100%	80 (63)	2 (5)	60 (48)	1 (2)
	60% to < 80%	6 (5)	0	6 (5)	0
	< 60%	1 (< 1)	1 (2)	4 (3)	0
	Missing	2 (2)	0	3 (2)	0

b.i.d. = twice daily; Fp MDPI = fluticasone propionate multidose dry powder inhaler; Fp HFA= fluticasone propionate hydrofluoroalkane; SD = standard deviation; n = total number of patients.

Source: Clinical study report.[8]

Critical Appraisal

Internal Validity

- In the included efficacy studies 301 and 30017, patient characteristics appear to have a some imbalances between treatment groups. In Study 301, there was a higher proportion of patients in the Fp MDPI 55 mcg group who were 65 years of age or older (18%) compared with those taking placebo and those in the Fp MDPI 113 mcg group (8% each). There was also a higher number of patients in the Fp MDPI 55 mcg group with a duration of asthma for one to five years (13%) in comparison with those taking placebo (9%) or in the Fp MDPI 113 mcg group (8%). In Study 30017, there was a higher proportion of patients previously taking montelukast in the Fp MDPI 113 mcg group (6%) compared with those in the placebo (2%) and those in the Fp MDPI 232 mcg group (3%). Montelukast is a leukotriene receptor antagonist, therefore its use was prohibited seven days before screening. Montelukast is considered a third-line drug for use in the treatment of asthma, and the fact that this medication discontinued before screening can lead to an unpredictable effect on asthma management.
- In the included safety Study 305, the majority of patients in all treatment groups were between 18 and 64 years of age, with the Flovent 220 mcg group containing the largest proportion of these patients (85%) relative to other groups (76%). Within the medium-strength cohort, 7% of patients in the Fp MDPI 113 mcg arm were concomitantly using montelukast, compared with 14% in the Fp HFA arm. Within the high-strength cohort,

12% of patients in the Fp MDPI 232 mcg arm were taking montelukast, compared with 7% in the Fp HFA 220 mcg arm. In this study, montelukast was not listed as a prohibited medication; however, it is possible that patients taking this medication have more advanced asthma, leading to an imbalance between treatment groups.

- The only study with an active comparator was an open-label study designed to be primarily a safety study, Study 305. This comparison was between Fp MDPI and another fluticasone propionate preparation, Fp HFA, and the efficacy outcome within this study was defined as change from baseline in trough FEV_1 at week 26. This efficacy outcome was defined a priori for which it had 90% power to determine noninferiority between the pooled medium- and high-dose arms of Fp MDPI and the pooled medium- and high-dose arms of Fp HFA. The noninferiority margin used was –0.125 L. There was no apparent rationale provided with this choice of noninferiority margin. However, the margin is approximately one-half of the MCID suggested by the Health Canada reviewer's report (0.2 L),[2] and the minimally perceivable improvement from baseline in trough FEV_1 reported in the literature (0.23 L),[31] which may be reasonable in the context of what appears to be a clinically derived noninferiority margin as per FDA guidance.[33] Results were presented for pooled doses with respect to this outcome, as well as for the separate arms comparing to Fp MDPI 113 mcg arm to the Fp HFA 110 mcg arm, and the Fp MDPI 232 mcg arm to the Fp HFA 220 mcg arm. These noninferiority analyses comparing the separate dosage arms of Fp MDPI to Fp HFA appear to have been performed ad hoc and do not seem to be adjusted for multiplicity, which would limit its interpretation.
- There was a higher rate of discontinuation in the placebo groups compared with the Fp MDPI groups for the 12-week efficacy trials, 301 and 30017. In the adjusted ANCOVA model used in the primary analysis, missing data caused by early dropout was imputed using the BOCF approach. This method assigned patients a change from baseline in trough FEV_1 score of zero, thus discontinued patients were to be treated as failures and therefore assigned a poor score. To impute missing FEV_1 values for these patients who discontinued treatment before week 12, tipping point sensitivity analyses were conducted. The results from the tipping point analysis appeared to support the primary end point conclusions; however, there is a risk that worsening FEV_1 values for patients who withdrew in the placebo group due to worsening asthma may not have been adequately captured, and thereby potentially biasing results in favour of Fp. Of note, the FDA statistical reviewer conducted several sensitivity analysis and concluded that these analyses agreed with the main analysis.[29]
- During the run-in period of the safety Study 305, patients were instructed to continue using their current ICS and/or other controller therapies, except for their short-acting beta-2 agonist inhaler to be used as needed for symptomatic relief of asthma symptoms, which was replaced with salbutamol/albuterol. As a result, patients did not discontinue their current ICS or ICS/LABA treatment until randomization, which may have introduced a risk of carry-over effects at the time of starting either Fp HFA or Fp MDPI. Although the half-life of both of these treatments is about eight hours, due to the lack of an adequate washout period it is difficult to rule out that any clinical changes seen in this study may be due to the patient initially being stable on their current ICS treatment.
- Studies 301 and 30017 were designed with the primary objective of establishing superiority of FS over Fp, followed by superiority of FS over placebo, and finally superiority of Fp over placebo. The order of statistical analysis hierarchy seems to have been established in line with the order of the study objectives. Also, the standardized baseline-adjusted FEV_1 AEUC 0-12 (not included in this review) was listed first in the

hierarchy despite the first primary end point for the study listed as change from baseline in trough FEV_1, the latter of which is more relevant for assessing the effects of ICS monotherapy. This does not affect the interpretation of the results. According to the FDA statistical analysis report for this drug,[29] the manufacturer's hierarchy approach for the analyses of secondary end points in studies 301 and 30017 controlled the type I error for comparisons at a particular study drug/strength, as well as comparisons over study drug/strengths within a particular end point; however, it did not control for overall type I error. It was noted in this report that the manufacturers were notified; however, their approach was not modified. Therefore, results for the secondary end points of these studies should be interpreted with this in mind.

- Hierarchy rules established a priori with regard to secondary outcomes did not appear to be implemented when presenting the results for Study 301, as the first secondary end point in the hierarchy (change from baseline in weekly average of daily trough morning PEF) did not meet the criteria for statistical significance of $P < 0.05$ for the comparison of Fp MDPI 55 mcg versus placebo.
- Inclusion criteria for efficacy studies 301 and 30017 stipulated that patients were required to meet specific qualifying dosages of equivalent ICS dosages (Table 6) based on previous ICS therapy. The qualifying dosages provided did not specify which dosages qualified as low, medium, and high ICS dosage ranges. Therefore, it was unclear how the decision was made to place patients into respective Fp MDPI 55 mcg, 113 mcg, and 232 mcg groups after inclusion criteria were met. The possibility of patients enrolled into either Study 301 being mismatched to a low-dose (55 mcg) or medium-dose (113 mcg) Fp MDPI group, or in Study 30017 being mismatched to a medium-dose (113 mcg) or high-dose (232 mcg) Fp MDPI group based on their previous ICS dosage cannot be ruled out.
- All efficacy analyses were based on the full analysis set, which included all patients who received any dose of study medication and had a nonmissing baseline and at least one nonmissing post-baseline trough FEV_1 measurement. A supportive primary analysis was conducted alongside the primary outcomes of all included studies with the ITT population, and the analyses were based on a population similar enough to that of an ITT as to have a low probability of materially having an impact on the validity of the analyses and findings of the studies.
- The efficacy studies were both double-blinded. However, placebo groups showed the highest rates of premature discontinuation, withdrawal due to lack of efficacy, disease progression, AEs (including asthma-related events), and short duration exposure, which may suggest that blinding might have been compromised in these groups. The majority of secondary outcomes in these studies were patient-reported; therefore, outcome assessment might be biased in favour of the active treatments. In addition, patients' knowledge of his/her treatment may have affected efforts placed on the spirometer testing, which has potential to raise uncertainty around the FEV_1 comparisons versus placebo.
- Before screening for the efficacy trials, patients were to discontinue their current asthma regimen including ICS or ICS/LABA treatment, and during the run-in period were instructed to take one inhalation of open-label QVAR 40 mcg HFA MDI twice daily in Study 301, and one inhalation of Fp MDPI 55 mcg twice daily in Study 30017. These are both considered to be low-dose ICS treatment. The clinical expert consulted for this study was concerned that these patients were suboptimally treated during this run-in period, and consequentially would produce falsely suboptimal values for FEV_1, use of rescue medication, AQLQ(S), and other efficacy outcomes at baseline. This would

ultimately over-estimate the treatment effect (change from baseline) of Fp MDPI in these studies.

- Many of the secondary efficacy outcome included in all studies, such as asthma symptom scores, AQLQ(S), ACTs, and use of rescue medication were diary-reported outcomes, therefore subjective to the patients involved. This issue is compounded by the fact that many patients in the placebo group may have been unblinded due to disease progression, which may have increased risk of bias in favour of treatment.

External Validity

- Fp MDPI delivers a lower nominal dose of fluticasone propionate than Flovent HFA (Fp HFA) as well as Flovent Diskus, and pharmacokinetic studies show that the systemic exposure of Fp MDPI is lower than or similar to Flovent Diskus.[16] However, there remains uncertainty as to whether Fp MDPI will elicit a similar level of efficacy to existing Fp preparations, due to the fact that both phase III efficacy studies were placebo-controlled, and only one efficacy outcome in the safety trial (versus Flovent HFA) was powered to detect noninferiority (not equivalence) in pooled dosage arms. Head-to-head comparisons were conducted in the phase II dose-ranging studies, Study 201 and Study 202 (Appendix 8), which found no statistically significant differences between Fp MDPI and Flovent Diskus for the change from baseline in trough FEV_1 at 12 weeks, though limitations associated with these studies mean there is uncertainty regarding the comparative efficacy. Furthermore, the safety outcomes in the safety trial have not demonstrated any discernable improvement compared with Fp HFA, and therefore it is unknown whether any long-term benefits can be seen from this reported reduced systemic exposure. The maximum dose in the product monograph for Fp MDPI is as 464 mcg (one inhalation of 232 mcg twice daily),[3] creating a concern that if a patient is not optimally treated on this dose, another preparation would need to be used. [redacted] As a result, equivalence with a comparator was not a consideration for Health Canada approval of Fp MDPI. Of note, requirements to establish efficacy with Health Canada given that the chemical composition is the same as another marketed product were different (i.e., placebo-controlled trials, of relatively shorter duration, with change in FEV_1 as the primary outcome).[5] The clinical expert consulted for this review also questioned whether the marketed dose for Fp MDPI would cause confusion among Canadian prescribers who are familiar with doses on current Flovent products. Moreover, the absence of steroid equivalency comparisons with ICS products other than ones containing fluticasone propionate makes comparing products extremely difficult.
- The patients enrolled in studies 301 and 30017 were predominantly female (58%), white (80%), and never smokers (86%), with a mean age of 43 years (range: 12 to 86 years). According to the clinical expert consulted for this review, these patients were older than the general asthma population in Canada, which may have had implications on the uptake of new medications, as well as adherence. Also, the overwhelming majority of patients in this study being Caucasian may limit the generalizability of these results to patients of other races.
- All identified trials recruited patients ≥ 12 years of age. In the all of the included studies, the proportion of adolescents was about 10% of the complete study population. As a

result, the extent to which the efficacy and safety outcomes would be affected by the higher proportion of younger patients is unknown. The interpretation of its effect in this population is not well-established.

- Overall, the trials had a relatively short duration: 12 weeks for the efficacy trials and 26 weeks for the safety trial. This is an inadequate length of time to assess the long-term efficacy and safety of a medication routinely used for a chronic condition such as asthma.
- Baseline asthma severity levels were evaluated by FEV_1, the pre-bronchodilator % predicted FEV_1 for the efficacy trials ranged from 66% to 68%. These values indicate that the included patients might have been suboptimally treated for their asthma before enrolment in the studies. Therefore, results might be biased in favour of the active treatment groups because patients in these groups would have their treatment dose improved while placebo patients would have their suboptimal active ICS switched to placebo.
- The safety trial, Study 305 compared Fp MDPI with Fp HFA MDI. The clinical expert involved in this review questioned the choice of comparator, due the different type of inhaler. The expert believed that without use of a spacer, it is difficult to assume that this inhaler technique would be consistent with an MDI when compared with a MDPI. Throughout the safety study, training was provided on either inhaler occurring weekly at randomization and at treatment visits; however, this would be difficult to extrapolate to the general asthma population where proper inhaler use may be suboptimal.
- The clinical expert consulted for this review noted the abnormally high rate of unscheduled medical visits (24% to 32%), emergency room or urgent care visits (10% to 17%), and hospitalizations (< 1% to 5%) observed in all arms in the 26-week safety Study 305. This raises concern as to whether this sample is reflective of the larger Canadian asthma patient population, and in turn how these results can be extrapolated to this larger population.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported below. See Appendix 4 for detailed efficacy data.

Spirometry End Points

Forced Expiratory Volume in One Second

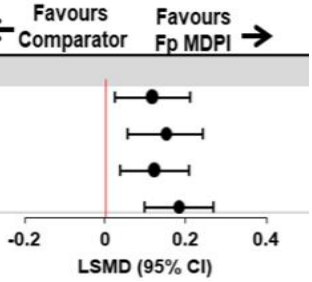
Change from baseline (Figure 4) in FEV_1 at 12 weeks was a co-primary end point of the two efficacy trials. As shown in all three dosage regimens of Fp MDPI were superior to placebo for change from baseline in FEV_1 at 12 weeks. Compared with placebo, the least squares mean differences were 0.119 L (95% CI, 0.025 to 0.212) and 0.151 L (95% CI, 0.057 to 0.244) for the 55 mcg twice daily and 113 mcg twice daily regimens in Study 301 and 0.123 L (95% CI, 0.038 to 0.208) and 0.183 L (95% CI, 0.098 to 0.268) for the 113 mcg twice daily and 232 mcg twice daily regimens in Study 30017. The primary analysis was conducted using the full analysis data set and the results were similar in the sensitivity analysis using the ITT population. The primary analysis was conducted using the full analysis data set and the results were similar in the sensitivity analysis using the ITT population.

In the safety study, there were similar results observed for the pooled analysis of Fp MDPI and Fp HFA groups for the efficacy assessment in this study. The change from baseline in

trough FEV_1 over the 26 week period was 0.069 L (95% CI, 0.035 to 0.104) in the Fp MDPI group and 0.071 L (95% CI, 0.013 to 0.129) in the Fp HFA group. This yielded a least squares mean change from baseline difference in trough FEV_1 of Fp MDPI from Fp HFA groups of –0.002 L (95% CI, –0.068 to 0.065). Therefore, the treatment effect and lower limit of the 95% confidence interval exceeded the –0.125 L noninferiority margin for FEV_1.

Figure 4: Change From Baseline in FEV_1 at 12 weeks and 26 weeks

Study	Comparison	LSM (SE) Fp MDPI	LSM (SE) Comparator	Comparison LSMD (95% CI)	Comparison P value
12 weeks					
301	Fp MDPI 55 mcg BID vs. Placebo	0. 172 (0.0347)	0.053 (0.0350)	0.119 (0.025, 0.212)	0.0132
	Fp MDPI 113 mcg BID vs. Placebo	0.204 (0.0340)	0.053 (0.0350)	0.151 (0.057, 0.244)	0.0017
30017	Fp MDPI 113 mcg BID vs. Placebo	0.119 (0.0311)	-0.004 (0.0312)	0.123 (0.038, 0.208)	0.0047
	Fp MDPI 232 mcg BID vs. Placebo	0.179 (0.0308)	-0.004 (0.0312)	0.183 (0.098, 0.268)	0.0000



Fp MDPI = fluticasone propionate multidose dry powder inhaler; b.i.d. = twice daily; CI = confidence interval; LSM = least squares mean; LSMD = least squares mean difference; SE = standard error.

Source: Clinical study reports.[6-8]

Table 22: Change From Baseline in Trough FEV_1 (L) Over the 26-week Treatment Period for Study 305

Change in Trough FEV_1 Over 26 Weeks	High-/Medium-Strength Doses Combined Fp MDPI 113 mcg b.i.d. and Fp MDPI 232 mcg b.i.d. (Fp MDPI b.i.d.) vs. Fp HFA 110 mcg b.i.d. and Fp HFA 220 mcg HFA b.i.d. (Fp HFA b.i.d.)	
	Fp MDPI b.i.d. (N = 243)	Fp HFA b.i.d. (N = 83)
LS mean	0.069	0.071
SE of LS mean	0.0175	0.0295
95% CI	(0.035 to 0.104)	(0.013 to 0.129)
Comparison of Fp MDPI to Fp HFA		
Difference of LS mean	–0.002	
95% CI	(–0.068 to 0.065)	
P value	0.9577	

b.i.d. = twice daily; CI = confidence intervals; FEV_1 = forced expiratory volume in one second; FP MDPI = fluticasone propionate multidose dry powder inhaler; Fp HFA = fluticasone propionate hydrofluoroalkane; LS = least squares.

Source: Clinical study reports.[8]

Sensitivity Analyses Results

The tipping point analysis results for both efficacy studies 301 and 30017 are presented in Table 23. In terms of change from baseline trough FEV_1, for the comparison of FS 232 mcg over placebo in Study 30017, the estimated treatment effect at week 12 was 0.183 L (95% CI, 0.098 to 0.268) from the modified-BOCF ANCOVA model, and the estimated treatment effect over the 12-week treatment period from the MMRM analysis based on observed data were 0.140 L. For most of the comparisons, an assumed shift in the missing data assumptions on the experimental treatment arm of roughly 4-fold (–0.39 versus 0.091 in Fp MDPI 113 mcg versus placebo in Study 30017) to 10-fold (–1.52 versus 0.140 in Fp 232 mcg versus placebo in Study 30017) times the size of the treatment effect would be needed

to tip the positive decision on treatment efficacy. With this consideration, the tipping point sensitivity analysis results confirmed the validity of the positive primary analysis results, which were based on missing data handling methods with the potential to violate the mechanism of truly unknown missing data.

Table 23: Tipping Point Analysis Results for Efficacy Studies for Change From Baseline in Trough FEV_1

Planned Comparison[a]	Primary Analysis Results (95% CI), *P* Value	Estimated Effect from MMRM Over a 12-Week Treatment Period (95% CI, *P* value)	Tipping Point
Study 301			
Fp MDPI 55 mcg vs. Placebo	0.119 (0.025 to 0.212) *P* = 0.013	0.136 (0.057 to 0.215) *P* < 0.001	–1.13
Fp MDPI 113 mcg vs. Placebo	0.151 (0.056 to 0.244) *P* = 0.002	0.150 (0.072 to 0.229) *P* < 0.001	–1.26
Study 30017			
Fp MDPI 113 mcg vs. Placebo	0.123 (0.038 to 0.208) *P* = 0.005	0.091 (0.023 to 0.159) *P* = 0.009	–0.39
Fp MDPI 232 mcg vs. Placebo	0.183 (0.098 to 0.268) *P* < 0.001	0.140 (0.072 to 0.208) *P* < 0.001	–1.52

ANCOVA = analysis of covariance; CI = confidence interval; FEV_1= forced expiratory volume in 1 second; Fp MDPI = fluticasone propionate multidose dry powder inhaler; MMRM = mixed model repeated measures; vs. = versus.

[a] Treatment comparisons and analysis is based on an ANCOVA model with adjustment for baseline FEV_1, sex, age, (pooled) centre, previous therapy (ICS or ICS/LABA), and treatment. Missing data are imputed using the modified BOCF.

Source: Clinical study reports.[6,7]

Asthma Symptoms

Results for change from baseline in the weekly average of the total daily asthma symptom score over weeks 1 to 12 are presented for studies 301 and 30017, and over weeks one to 26 for Study 305, in Table 24. All treatment arms, including placebo, saw an overall reduction in asthma symptom scores over time. With regard to the efficacy studies, there was a statistically significant improvement observed for the Fp MDPI 113 mcg arm and the Fp MDPI 232 mcg arm relative to placebo in Study 30017. Statistical significance for differences observed in the Fp MDPI 55mcg group versus placebo in Study 301 cannot be concluded in accordance with the fixed-sequence testing procedure, which failed at the change from baseline in weekly average of the daily trough morning PEF.

In the Study 305, LS mean changes from baseline in asthma symptom scores were observed to be similar between the Fp MDPI and Fp HFA groups at both strengths over the 26-week treatment period.

Table 24: Total Daily Asthma Symptom Scores in All Included Studies

Study	Treatment Group	Baseline Mean (SE)	End Point Mean (SE)	LS Mean (SE) [95% CI]	LSMD (95% CI)	Fp MDPI vs. Placebo (*P* value)
301	Placebo (N = 129)	0.796 (0.0356)	0.652 (0.0522)	–0.135 (0.0318) [–0.197 to –0.072]	—	—
	Fp MDPI 55 mcg b.i.d. (N = 128)	0.825 (0.0423)	0.503 (0.0490)	–0.278 (0.0314) [–0.340 to –0.216]	–0.143 (–0.229 to –0.058)	0.0010 [a]
	Fp MDPI 113 mcg b.i.d. (N = 129)	0.782 (0.0395)	0.425 (0.0398)	–0.300 (0.0308) [–0.361 to –0.240]	–0.165 (–0.251 to –0.080)	0.0002
30017	Placebo (N = 143)	0.881 (0.0470)	0.810 (0.0599)	–0.087 (0.0342) [–0.154 to –0.020]	—	—
	Fp MDPI 113 mcg b.i.d. (N = 145)	0.804 (0.0409)	0.520 (0.0411)	–0.282 (0.0333) [–0.347 to –0.217]	–0.195 (–0.288 to –0.102)	< 0.0001
	Fp MDPI 232 mcg b.i.d. (N = 146)	0.900 (0.0424)	0.622 (0.6581)	–0.242 (0.0329) [–0.307 to –0.178]	–0.156 (–0.248 to –0.063)	0.0010
305	Fp MDPI 113 mcg b.i.d. (N = 123)	0.588 (0.0546)	0.429 (0.0479)	–0.077 (0.0271) [–0.130 to –0.024]	—	—
	Fp HFA 110 mcg b.i.d. (N = 42)	0.517 (0.0845)	0.437 (0.0758)	–0.072 (0.0468) [–0.164 to 0.020]	—	—
	Fp MDPI 232 mcg b.i.d. (N = 120)	0.431 (0.0435)	0.224 (0.0300)	–0.155 (0.0275) [–0.209 to –0.101]	-—	—
	Fp HFA 220 mcg b.i.d. (N = 41)	0.535 (0.1015)	0.342 (0.5040)	–0.139 (0.0468) [–0.231 to –0.047]	-—	—

Fp MDPI = fluticasone propionate multidose dry powder inhaler; b.i.d. = twice daily; CI = confidence interval; LSM = least squares mean; LSMD = least squares mean difference; SE = standard error.

[a] The hierarchical statistical testing procedure stopped at a higher order comparison; therefore, these findings are considered hypothesis generating.

Source: Clinical study reports.[6-8]

Total Daily Use of Rescue Medication

Table 24 presents results for the change from baseline in weekly average of the total daily use of albuterol/salbutamol over the course of the 12-week treatment period for studies 301 and 30017. In Study 301, statistical significance for differences observed in the Fp MDPI 55 mcg group cannot be concluded in accordance with the fixed-sequence testing procedure, due to the hierarchical procedure failing at a higher order comparison.

In Study 30017, both treatment arms showed a greater decrease in the weekly mean number of inhalations per day of rescue medication compared with placebo (Fp MDPI 113 mcg: LS mean change –0.439 inhalations/day, $P = 0.0001$; Fp MDPI 232 mcg: LS mean change –0.534 inhalations/day, $P < 0.0001$).

Table 25: Summary of Change From Baseline in Weekly Average of the Total Daily Use of Albuterol/Salbutamol

Comparison	Study 301			Study 30017		
	Placebo	Fp MDPI 55 mcg b.i.d.	Fp MDPI 113 mcg b.i.d.	Placebo	Fp MDPI 113 mcg b.i.d.	Fp MDPI 232 mcg b.i.d.
N	129	128	129	143	145	146
Baseline number of inhalations, (SE)	1.4 (0.11)	1.3 (0.10)	1.2 (0.11)	1.7 (0.15)	1.6 (0.13)	1.8 (0.13)
Change from Baseline LS mean (SE)	–0.003 (0.0937)	–0.467 (0.0928)	–0.466 (0.0915)	0.168 (0.1102)	–0.439 (0.1081)	–0.534 (0.1070)
Comparison to Placebo (95% CI)	—	–0.464 (–0.718 to –0.211)	–0.463 (–0.716 to –0.209)	—	–0.607 (–0.908 to –0.307)	–0.702 (–1.001 to –0.403)
P value	—	0.0003[a]	0.0004	—	0.0001	< 0.0001

b.i.d. = twice daily; CI = confidence intervals; Fp MDPI = fluticasone propionate multidose dry powder inhaler; SE = standard error.

[a] The hierarchical statistical testing procedure stopped at a higher order comparison; therefore, these findings are considered hypothesis generating.

Source: Clinical study reports.[6,7]

The proportions of patients experiencing asthma exacerbations are presented in Table 26. For Study 301, four patients in the placebo group and one patient each in the 55 mcg and 113 mcg Fp MDPI groups were withdrawn due to asthma exacerbation during 12 weeks of study. Four patients in the placebo group all experienced moderate asthma exacerbations, and withdrew due to worsening asthma from day 8 to day 45. The patient in the Fp MDPI 55 mcg group experienced a moderate asthma exacerbation beginning at day 65 and later withdrew due to lack of efficacy. The patient in the Fp MDPI 113 mcg group experienced a moderate exacerbation beginning on day 44 and later withdrew due to disease progression.

For Study 30017, 20 patients in the placebo group, one patient in the Fp 113 mcg group, and three patients in the Fp 232 mcg group withdrew due to asthma exacerbation during the 12-week study. Exacerbations occurred for placebo patients beginning on days 2 to 85, and for patients on Fp MDPI beginning on days 10 to 86 of the 12-week treatment period. The one patient in the Fp MDPI 113 mcg group experienced a severe asthma exacerbation beginning at day 10, and the three patients in the Fp MDPI 232 mcg group experienced mild to moderate asthma exacerbations ranging from day 29 to day 68.

Table 26: Patient Withdrawal for Worsening Asthma Over 12-week Treatment Period

Comparison	Placebo/ Fp HFA		Fp MDPI		Fp MDPI vs. Placebo *P* value[b]
	Events n (%)	Censored[a] n (%)	Events n (%)	Censored n (%)	
301					
Fp MDPI 55 mcg b.i.d. vs. Placebo	4 (3)	125 (97)	1 (< 1)	127 (> 99)	0.1707
Fp MDPI 113 mcg b.i.d. vs. Placebo	4 (3)	125 (97)	1 (< 1)	128 (> 99)	0.1679
30017					
Fp MDPI 113 mcg b.i.d. vs. Placebo	20 (14)	123 (86)	1 (< 1)	144 (>99)	< 0.0001
Fp MDPI 232 mcg b.i.d. vs. Placebo	20 (14)	123 (86)	3 (2)	143 (98)	0.0001

b.i.d. = twice daily; Fp HFA = fluticasone propionate hydrofluoroalkane; FP MDPI = fluticasone propionate multidose dry powder inhaler.

[a] Patients who completed the study, who were lost to follow-up, or who had not had a severe asthma exacerbation by week 12 were right-censored at the date of the assessment.

[b] *P* value is based on the log-rank test for pairwise comparisons of FP MDPI and placebo.

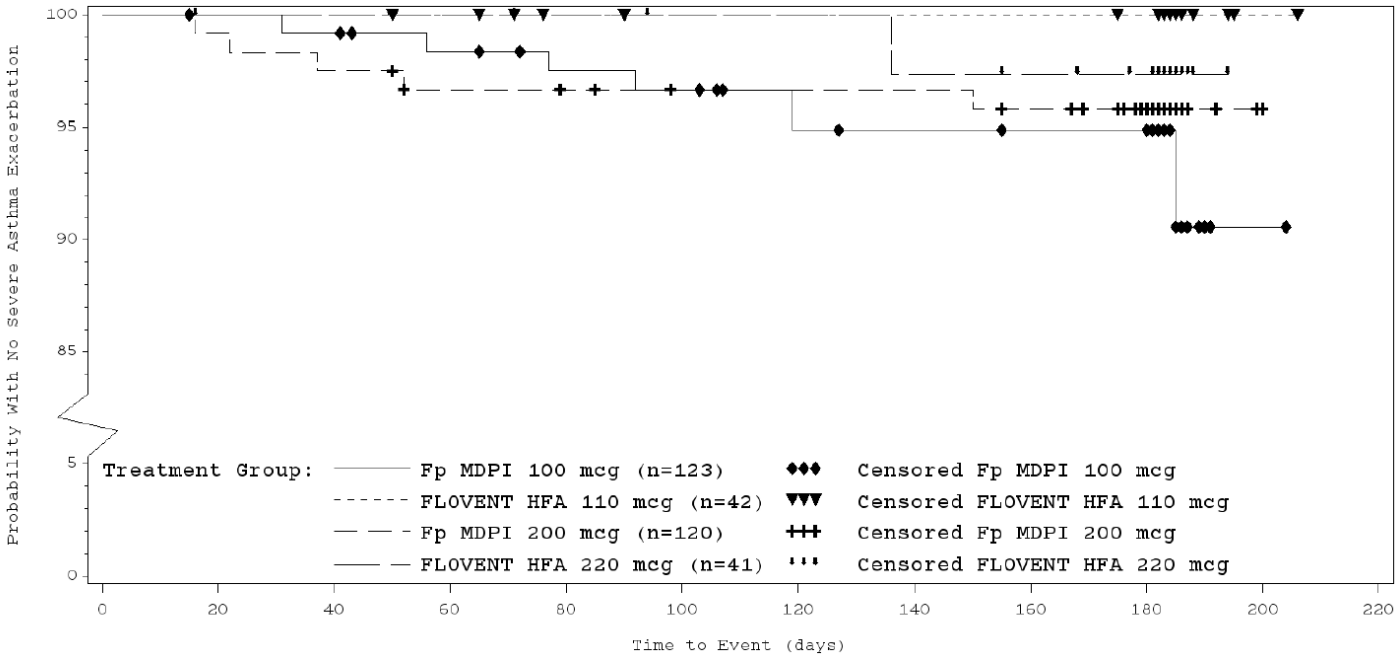
Source: Clinical study reports.[6-8]

The limited number of asthma exacerbation events prevented time-to-event analysis, and medians were not estimable in Study 301.

For Study 30017, both Fp MDPI groups were statistically significantly superior to those in the placebo group for time to patient withdrawal for asthma exacerbations during the 12-week treatment period (log-rank test: $P < 0.0001$ for Fp MDPI 113 mcg and $P = 0.0001$ for Fp MDPI 200 mcg; Kaplan-Meier curve was not reported in the clinical study report).

In Study 305, time-to-event analysis was conducted for severe asthma exacerbations. Median times to first severe asthma exacerbation were not estimable because of the limited number of events, defined as one that required systemic corticosteroid us for ≥ three days or hospitalization or an emergency department visit due to asthma requiring treatment with systemic corticosteroids. The frequency of severe asthma was numerically greater among patients treated with Fp MDPI 113 mcg than among those treated with Fp HFA at 110 mcg (seven [6%] and zero patients, respectively), and this difference was slightly smaller at the high-strength (5 [4%] and 1 [2%] patients, respectively). One severe asthma exacerbation in the Fp MDPI 232 mcg group required hospitalization on day 15 and resolved on day 23.Kaplan-Meier curves no statistically significant differences between times to event for asthma exacerbations among patients treated with Fp MDPI than among patients treated with Fp HFA during the 26-week treatment period (log-rank test: $P = 0.1304$ for Fp MDPI 113 mcg versus Fp HFA 110 mcg and $P = 0.6250$ for Fp MDPI 232 mcg versus Fp HFA 220 mcg, see Figure 5).

Figure 5: Kaplan-Meier Curve for Time to First Severe Asthma Exacerbation Event During the 26-week Treatment Period



Fp MDPI = Fluticasone propionate multidose dry powder inhaler; b.i.d. = twice daily; HFA = hydrofluoroalkane.

Note: Dosing of Fp MDPI and FS MDPI were referred to in the figures above by their nominal doses. Their metered doses are 55mcg, 113mcg, and 232mcg for Fp MDPI, and 55/12.5mcg, 113/12.5mcg and 232/12.5 mcg for FS MDPI. These products have been referred to by their metered doses in this report.

Source: Clinical study reports.[8]

Health-Related Quality of Life

For both studies 301 and 30017, the studies and treatment arms were similar across groups at baseline for AQLQ(S) or PAQLQ(S) scores with a mean score range of 4.921 to 5.151.

At the end of the 12-week double-blind treatment period in Study 301, the mean AQLQ(S) score was found to have improved from baseline versus placebo in both Fp MDPI groups. However, hierarchical testing was stopped before this outcome in the Fp MDPI 55 mcg group and so the results were considered as hypothesis generating (Table 27).

In Study 30017, the treatment arm Fp MDPI 113 mcg showed no statistically significant improvement in AQLQ(S) score at the end of the 12-week treatment period versus placebo (P = 0.1962). There was a statistically significant improvement observed at the end of 12 weeks in the Fp MDPI 232 mcg treatment arm versus placebo for this outcome (LS mean change, 0.216; 95% CI, 0.017 to 0.415; P = 0.0334); however this difference did not approach the ≥0.5 MCID to be considered clinically significant.

The sample sizes of adolescent patients within treatment groups who completed the PAQLQ(S) were small in both trials, ranging from 12 to 19 patients in Study 301, and six to 12 patients in Study 30017. As a result, mean changes from baseline at week 12 were summarized separately and not entered into the statistical analysis. In Study 301, the mean

changes in PAQLQ(S) scores from baseline at week 12 were 0.761 for adolescents taking placebo, 0.362 for those in the Fp MDPI 55 mcg group, and 0.500 for those in the Fp MDPI 113 mcg group. In Study 30017, the mean changes in PAQLQ(S) scores from baseline at week 12 were 0.587 for those taking placebo, 0.935 for those in the Fp MDPI 113 mcg group, and 0.800 for those in the Fp MDPI 232 mcg group.

Table 27: Change From Baseline in AQLQ(S) in Studies 301 and 30017

Study	Treatment Group	Baseline Mean (SE)	End Point Mean (SE)	LS Mean (SE) [95% CI]	LSMD (95% CI)	Fp MDPI vs. Placebo (*P* value)
301	Placebo (N = 129)	4.921 (0.0958)	5.192 (0.0949)	0.335 (0.0777) [0.183, 0.488]	—	—
	FP MDPI 55 mcg b.i.d. (N = 128)	5.151 (0.0975)	5.676 (0.0932)	0.588 (0.0733) [0.444, 0.732]	0.253 (0.048 to 0.458)	0.0155
	FP MDPI 113 mcg b.i.d. (N = 129)	5.025 (0.0799)	5.617 (0.0830)	0.636 (0.0736) [0.492, 0.781]	0.301 (0.094 to 0.508)	0.0044
30017	Placebo (N = 143)	4.924 (0.0794)	4.814 (0.1025)	0.203 (0.0761) [0.053, 0.352]	-—	—
	FP MDPI 113 mcg b.i.d. (N = 145)	5.024 (0.0820)	5.285 (0.0838)	0.334 (0.0683) [0.200, 0.468]	0.131 (–0.068 to 0.330)	0.1962
	FP MDPI 232 mcg b.i.d. (N = 146)	4.941 (0.0796)	5.312 (0.0919)	0.418 (0.0685) [0.284, 0.553]	0.216 (0.017 to 0.415)	0.0334

AQLQ(S) = Asthma Quality of Life Questionnaire With Standardized Activities; b.i.d. = twice daily; CI = confidence interval; FP MDPI = fluticasone propionate multidose dry powder inhaler; LS = least squares; LSMD = least squares mean difference; MDPI = multidose dry powder inhaler; SE = standard error.

Source: Clinical study reports.

Asthma Control Test

In Study 301, baseline ACT scores were similar across treatment groups at approximately 17 points. Results for the mean changes from baseline in ACT scores in both Fp MDPI treatment groups were statistically significantly higher than those in the placebo group over the 12-week treatment period at the end point. (Table 28). In Study 30017, baseline ACT scores were also similar across treatment groups (approximately 16 points). ACT scores in both Fp MDPI treatment groups over the 12-week treatment were also found to be statistically significantly higher than those in the placebo group. Statistical testing for this outcome was considered exploratory, as this outcome was not included in the hierarchical analysis plan for either study.

Within the included arms of Study 305, the least squares mean changes from baseline in ACT scores were not statistically different between Fp MDPI groups and Fp HFA groups at both treatment strengths.

Table 28: Total Asthma Control Test Scores in All Included Studies

Study	Treatment Group	Baseline Mean (SE)	End Point Mean (SE)	LS Mean (SE) [95% CI]	LSMD (95% CI)	Fp MDPI vs Placebo (*P* Value)
301	Placebo (N = 129)	16.6 (0.31)	18.2 (0.38)	0.831 (0.2631) [0.314, 1.348]	—	—
	Fp MDPI 55 mcg b.i.d. (N = 128)	16.9 (0.32)	20.0 (0.33)	2.153 (0.2609) [1.641, 2.665]	1.322 (0.615 to 2.029)	0.0003
	Fp MDPI 113 mcg b.i.d. (N = 129)	16.9 (0.28)	19.8 (0.28)	2.251 (0.2574) [1.746, 2.756]	1.420 (0.711 to 2.129)	0.0001
30017	Placebo (N = 143)	16.3 (0.28)	16.3 (0.41)	0.151 (0.3069) [-0.451, 0.754]	—	—
	Fp MDPI 113 mcg b.i.d. (N = 145)	16.4 (0.28)	18.6 (0.29)	2.464 (0.3047) [1.865, 3.062]	2.312 (1.473 to 3.151)	< 0.0001
	Fp MDPI 232 mcg b.i.d. (N = 146)	16.2 (0.27)	18.3 (0.35)	2.109 (0.3027) [1.515, 2.703]	1.958 (1.121 to 2.794)	< 0.0001
305	Fp MDPI 113 mcg b.i.d. (N = 123)	18.9 (0.33)	20.9 (0.37)	1.010 (0.1954) [0.626, 1.393]	—	—
	Fp HFA 110 mcg b.i.d. (N = 42)	18.1 (0.68)	21.2 (0.43)	0.747 (0.3381) [0.083, 1.411]	—	—
	Fp MDPI 232 mcg b.i.d. (N = 120)	19.5 (0.32)	20.3 (0.36)	1.511 (0.1975) [1.123, 1.899]	—	—
	Fp HFA 220 mcg b.i.d. (N = 41)	18.8 (0.74)	20.1 (0.44)	1.091 (0.3381) [0.427, 1.755]	—	—

b.i.d. = twice daily; CI = confidence interval; FP MDPI = fluticasone propionate multidose dry powder inhaler; LSM = least squares mean; LSMD = least squares mean difference; SE = standard error.

Source: Clinical study reports.[6-8]

Health Care Resource Utilization

Health care resource utilization was reported in Study 305. Reports of unscheduled or outpatient visits were high across all treatment arms. In this study, additional resources were reported for both emergency department/urgent care facility visits and hospital visits over the 26 week treatment duration (Table 29). The number of visits were similar across groups.

During 26 weeks of treatment, the proportions of patients who had an unscheduled or outpatient visit were similar in the Fp MDPI and Fp HFA groups, and the numbers of visits per patient were similar as well. The number of patients who had an emergency department, urgent care, or a hospital visit was also similar between groups. Hospitalization for severe asthma exacerbation occurred in one of these patients, belonging to the Fp MDPI 232 mcg arm. (Table 29).

Table 29: Health Care Utilization Over 26 weeks, Study 305

End Points	Fp MDPI 113 mcg b.i.d. (N = 123)	Fp HFA 110 mcg b.i.d. (N = 42)	Fp MDPI 232 mcg b.i.d. (N = 120)	Fp HFA 220 mcg b.i.d. (N = 41)
Patients with an unscheduled or outpatient visit				
Patients with visit, n (%)	30 (24)	12 (29)	38 (32)	11 (27)
Number of visits	46	20	46	15
Mean (SE)	2 (0.2)	2 (0.3)	1 (0.1)	1 (0.2)
Median (range)	1 (1 to 5)	2 (1 to 4)	1 (1 to 3)	1 (1 to 3)
Patients with an emergency department or urgent care facility visit				
Patients with visit, n (%)	17 (14)	7 (17)	17 (14)	4 (10)
Number of visits	21	10	20	5
Mean (SE)	1 (0.1)	1 (0.4)	1 (0.1)	1 (0.3)
Median (range)	1 (1 to 3)	1 (1 to 4)	1 (1 to 2)	1 (1 to 2)
Patients with a hospital visit				
Patients with visit, n (%)	1 (< 1)	2 (5)	4 (3)	2 (5)
Number of visits	2	4	5	4
Mean (SE)	2 (0.0)	2 (0.0)	1 (0.3)	2 (0.0)
Median (range)	2 (2 to 2)	2 (2 to 2)	1 (1 to 2)	2 (2 to 2)

b.i.d. = twice daily; Fp HFA = fluticasone propionate hydrofluoroalkane; Fp MDPI = fluticasone propionate multidose dry powder inhaler; SE = standard error.

Source: Clinical study reports.[8]

Rescue Medication, Symptom-free, and Asthma Control Days

Baseline mean percentages of rescue-free 24-hour periods varied widely between efficacy studies 301 and 30017, ranging from 33.0% to 44.5% across both studies, and for safety Study 305, ranging from 58.2% to 65.5%. Similar ranges of values were seen in the baseline percentage of symptom-free days, with 13.9% to 19.2% in studies 301 and 30017, compared with 43.8% to 52.1% in Study 305. This is likely because the run-in period for studies 301 and 30017 had patients discontinued their current asthma regimen and instructed to take low-dose ICS treatment, differed from Study 305 where patients did not discontinue their prior asthma medication during this period. Statistical testing for this outcome was considered exploratory as this end point was not included in the statistical testing hierarchy.

For Study 301, there were no significant differences observed in the percentage of rescue-free 24-hour periods from baseline over the 12-week treatment period in either of the Fp MDPI groups compared than with the placebo group. For Study 30017 however, a significant difference for this outcome was observed with the Fp MDPI 113 mcg twice daily versus placebo ($P = 0.0002$) and Fp MDPI 232 mcg twice daily versus placebo ($P < 0.0001$). For Study 305, there were similar increases in the percentage of rescue-free 24-hour periods between Fp MDPI groups and Fp HFA groups.

There was an increase in the percentage of symptom-free 24-hour periods of Fp MDPI groups relative to placebo from baseline over the 12-week treatment periods in Study 30017, which was statistically significant in both Fp MDPI 113 mcg ($P = 0.0047$) and Fp MDPI 232 mcg ($P = 0.0013$) groups relative to placebo. In Study 301, there were no significant differences observed for this outcome. For the safety study, changes from baseline in the percentage of symptom-free 24-hour periods were similar between the Fp MDPI and Fp HFA groups.

For efficacy trials, baseline percentages for asthma control 24-hour periods (defined as 24-hour periods with asthma symptom scores of zero and no rescue medication usage) ranged from 10.8% to 13.0% and were similar across groups. Changes from baseline in these percentages were statistically significant for three of the four Fp MDPI treatment groups.

Table 30: Analysis of Change From Baseline in the Percentage of Rescue-free, Symptom-Free, and Asthma Control 24-Hour Periods During the 12-Week and 26-Week Trials

Study	Treatment Group	Baseline Mean (SE)	Change from Baseline		Fp MDPI Versus Placebo (*P* Value)[a]
			Mean (SE)	Median	
Percentage of Rescue-Free Days					
301	Placebo (N = 129)	39.6 (3.01)	21.0 (3.08)	13.7	NA
	FP MDPI 55 mcg b.i.d. (N = 128)	41.7 (3.17)	29.0 (3.40)	26.6	0.0806
	FP MDPI 113 mcg b.i.d. (N = 129)	44.5 (3.18)	22.8 (2.96)	14.6	0.4730
30017	Placebo (N = 143)	40.2 (2.86)	8.2 (2.47)	1.5	NA
	FP MDPI 113 mcg b.i.d. (N = 145)	40.2 (2.91)	21.5 (2.71)	18.0	0.0002
	FP MDPI 232 mcg b.i.d. (N = 146)	33.0 (2.77)	24.4 (2.42)	23.6	0.0000
305	Fp MDPI 113 mcg b.i.d. (N = 123)	65.2 (3.35)	8.4 (2.51)	0.0	-—
	Fp HFA 110 mcg b.i.d. (N = 42)	58.2 (6.56)	9.3 (3.84)	0.0	-—
	Fp MDPI 232 mcg b.i.d. (N = 120)	65.5 (3.25)	11.9 (2.48)	3.3	-—
	Fp HFA 220 mcg b.i.d. (N = 41)	61.6 (6.28)	7.0 (3.66)	2.2	-—
Percentage of Symptom-Free Days					
301	Placebo (N = 129)	13.9 (1.85)	21.7 (3.01)	4.8	NA
	FP MDPI 55 mcg b.i.d. (N = 128)	17.6 (2.16)	26.7 (3.12)	18.6	0.1060
	FP MDPI 113 mcg b.i.d. (N = 129)	18.1 (2.17)	25.3 (2.72)	19.3	0.0596
30017	Placebo (N = 143)	17.3 (2.06)	10.2 (2.44)	2.1	NA
	FP MDPI 113 mcg b.i.d. (N = 145)	19.2 (2.23)	19.9 (2.50)	13.3	0.0047
	FP MDPI 232 mcg b.i.d. (N = 146)	16.2 (2.05)	20.3 (2.36)	10.8	0.0013
305	Fp MDPI 113 mcg b.i.d. (N = 123)	43.8 (3.72)	9.4 (2.22)	1.1	-—
	Fp HFA 110 mcg b.i.d. (N = 42)	50.0 (6.52)	6.4 (4.48)	0.0	-—
	Fp MDPI 232 mcg b.i.d. (N = 120)	52.1 (3.55)	11.8 (2.77)	1.9	-—
	Fp HFA 220 mcg b.i.d. (N = 41)	51.4 (6.18)	8.2 (4.65)	2.9	-—
Asthma-Control 24-Hour Periods					
301	Placebo (N = 129)	10.8 (1.63)	22.2 (3.02)	3.2	NA
	FP MDPI 55 mcg b.i.d. (N = 128)	11.1 (1.43)	29.2 (3.04)	22.0	0.0461
	FP MDPI 113 mcg b.i.d. (N = 129)	12.6 (1.71)	25.7 (2.73)	19.4	0.1309

Study	Treatment Group	Baseline Mean (SE)	Change from Baseline		Fp MDPI Versus Placebo (*P* Value)[a]
			Mean (SE)	Median	
30017	Placebo (N = 143)	11.0 (1.46)	11.9 (2.17)	1.2	NA
	FP MDPI 113 mcg b.i.d. (N = 145)	13.0 (1.85)	22.1 (2.48)	13.9	0.0046
	FP MDPI 232 mcg b.i.d. (N = 146)	10.4 (1.54)	21.4 (2.39)	9.9	0.0030

b.i.d. = twice daily; FP MDPI = fluticasone propionate multidose dry powder inhaler; NA = not available; SE = standard error.

[a] Statistical testing for these outcomes is considered exploratory as none of these end points were included in the statistical testing hierarchy.

Source: Clinical study reports.[6-8]

Within the ICS cohorts, the mean numbers of rescue medication-free days were similar between the Fp MDPI and the Fp HFA groups at both strengths (Table 31). The mean changes from baseline in the weekly average of the numbers and percentages of rescue medication-free days were also comparable between the two treatment groups for each cohort. The proportion of patients who used rescue medications were fairly similar between the Fp MDPI and Fp HFA groups.

Table 31: Summary of Rescue Medication Used During the 26-week Treatment Period for Worsening Asthma

Treatment Group	Medication Days			Rescue Medication Taken (Puffs)			Change From Baseline In Weekly Average Of Rescue-Free Days		
	n	Mean (SE)	Median	n	Mean (SE)	Median	n	Mean (SE)	Median
FP MDPI 113 b.i.d.	5	21 (9.5)	15	13	31 (8.8)	18	123	0.6 (0.18)	0.0
Fp HFA 110 b.i.d.	1	7 (NA)	7	3	44 (13.9)	44	42	0.6 (0.27)	0.0
FP MDPI 232 b.i.d.	3	7 (1.0)	8	10	49 (12.5)	40	118	0.8 (0.17)	0.2
Fp HFA 220 b.i.d.	1	10 (NA)	10	3	21 (14.8)	10	41	0.5 (0.26)	0.2

b.i.d. = twice daily; Fp HFA = fluticasone propionate hydrofluoroalkane; FP MDPI = Fluticasone propionate multidose dry powder inhaler; NA = not available; SE = standard error.

Source: Clinical study reports.[8]

Harms

Only those harms identified in the review protocol are reported (see the Protocol section).

Adverse Events

The most frequently reported AEs reported were similar across both 12-week, efficacy trials. These included nasopharyngitis, cough, and upper respiratory tract infections (URTIs). In Study 301, 214 patients (33% of 641 in the safety population) experienced at least one AE during the study. The most frequently reported AEs in this study overall were nasopharyngitis, cough, and URTIs. Other frequently occurring AEs are shown in Table 32. Oral candidiasis was reported as an AE for one patient in the placebo group and seven patients in the active treatment groups; oropharyngeal pain was reported for three patients in the placebo group and two patients in the active treatment groups. Otherwise, nasopharyngitis occurred in relatively high proportions of patients in the Fp MDPI 113 mcg (7%) relative to the other groups (4% to 7%). There was an apparent imbalance between the placebo and active treatment groups for the system organ class of musculoskeletal and connective tissue disorders. In Study 30017, URTIs, oral candidiasis, and headache

occurred slightly more frequently with one or both doses of Fp MDPI compared with placebo (Table 32).

Table 32: Adverse Events in ≥ 2% of Patients in the Efficacy Trials

Adverse Events, n (%)	Study 301			Study 30017		
	Placebo (N = 129)	Fp MDPI 55 mcg b.i.d. (N = 129)	Fp MDPI 113 mcg b.i.d. (N = 129)	Placebo (N = 144)	Fp MDPI 113 mcg b.i.d. (N = 145)	Fp MDPI 232 mcg b.i.d. (N = 146)
Any TEAE	47 (36)	44 (34)	40 (31)	52 (36)	53 (37)	60 (41)
Gastrointestinal disorders	11 (9)	3 (2)	3 (2)	NR	NR	NR
Nausea	3 (2)	1 (< 1)	1 (<1)	NR	NR	NR
Abdominal pain upper	1 (< 1)	0	1 (<1)	NR	NR	NR
Infections and infestations	19 (15)	24 (19)	18 (14)	31 (22)	29 (20)	42 (29)
URTIs	6 (5)	7 (5)	4 (3)	7 (5)	9 (6)	8 (5)
Nasopharyngitis	4 (3)	7 (5)	9 (7)	8 (6)	7 (5)	7 (5)
Pharyngitis	3 (2)	1 (< 1)	0	2 (1)	0	3 (2)
Oral candidiasis	1 (< 1)	4 (3)	3 (2)	1 (< 1)	5 (3)	7 (5)
Respiratory tract infection	1 (< 1)	0	0	0	1 (< 1)	3 (2)
Sinusitis	1 (< 1)	1 (< 1)	0	3 (2)	3 (2)	2 (1)
Acute sinusitis	NR	NR	NR	3 (2)	0	0
Viral URTIs	1 (< 1)	2 (2)	0	3 (2)	0	2 (1)
Bronchitis	NR	NR	NR	7 (5)	3 (2)	3 (2)
Influenza	NR	NR	NR	1 (< 1)	2 (1)	2 (1)
Musculoskeletal and CTDs	1 (< 1)	3 (2)	5 (4)	6 (4)	4 (3)	7 (5)
Back pain	0	0	2 (2)	5 (3)	2 (1)	2 (1)
Myalgia	0	1 (< 1)	0	NR	NR	NR
Pain in extremity	0	0	2 (2)	NR	NR	NR
Nervous system disorders	5 (4)	3 (2)	11 (9)	7 (5)	14 (10)	9 (6)
Headache	5 (4)	2 (2)	9 (7)	7 (5)	11 (8)	7 (5)
Dizziness	0	1 (< 1)	2 (2)	NR	NR	NR
RTM disorders	10 (8)	14 (11)	6 (5)	11 (8)	8 (6)	12 (8)
Cough	3 (2)	2 (2)	4 (3)	4 (3)	1 (< 1)	5 (3)
Oropharyngeal pain	3 (2)	2 (2)	1 (< 1)	1 (< 1)	1 (< 1)	3 (2)
Asthma	2 (2)	0	0	NR	NR	NR
Dysphonia	2 (2)	2 (2)	0	NR	NR	NR
Nasal congestion	1 (< 1)	1 (< 1)	0	NR	NR	NR
Rhinitis allergic	1 (< 1)	0	1 (< 1)	1 (< 1)	3 (2)	1 (< 1)
Epistaxis	0	2 (2)	1 (< 1)	NR	NR	NR
Rhinorrhea	0	2 (2)	0	NR	NR	NR
Skin and SC disorders	1 (< 1)	1 (< 1)	2 (2)	NR	NR	NR

b.i.d. = twice daily; CTD = connective tissue disorders; FP MDPI = fluticasone propionate multidose dry powder inhaler; NR = not reported; RTM = respiratory, thoracic, and mediastinal; SC= subcutaneous; TEAE = treatment-emergent adverse event; URTI = upper respiratory tract infection.

Source: Clinical study reports.[6,7]

In the active-control Study 305, higher percentages were reported in the 26-week, safety trial, which was consistent with its longer duration. AEs were similar, reported as 66% to 67% of patients in the Fp MDPI group and 69% to 71% of the Fp HFA group (Table 33). The most commonly reported AEs were nasopharyngitis, URTIs, and oropharyngeal pain. The system organ classes with the highest incidence of AEs were infections and infestations (42% to 59%); respiratory, thoracic, and mediastinal disorders (17% to 28%); and musculoskeletal and connective tissue disorders (5% to 12%). The majority of the treatment-emergent adverse events occurring in Study 305 were judged by the investigators to be mild or moderate in severity, and deemed to be unrelated to the study drug. The higher incidence of AEs is most likely due to its longer study duration of 26 weeks.

Table 33: Adverse Events in ≥ 3% of Patients in the Safety Trial

Adverse Events, n (%)	Fp MDPI 113 mcg b.i.d. (N = 127)	Fp HFA 110 mcg b.i.d. (N = 42)	Fp MDPI 232 mcg b.i.d. (N = 125)	Fp HFA 220 mcg b.i.d. (N = 41)
Patients with at least 1 TEAE	85 (67)	29 (69)	83 (66)	29 (71)
Gastrointestinal disorders	14 (11)	6 (14)	7 (6)	5 (12)
Nausea	2 (2)	1 (2)	2 (2)	1 (2)
Vomiting	1 (< 1)	2 (5)	1 (< 1)	0
Toothache	1 (< 1)	0	1 (< 1)	2 (5)
General disorders and administration site conditions	9 (7)	2 (5)	9 (7)	2 (5)
Pyrexia	3 (2)	1 (2)	3 (2)	0
Infections and infestations	70 (55)	24 (57)	53 (42)	24 (59)
Upper respiratory tract infection	23 (18)	12 (29)	17 (14)	8 (20)
Sinusitis	15 (12)	3 (7)	6 (5)	3 (7)
Nasopharyngitis	17 (13)	7 (17)	13 (10)	5 (12)
Bronchitis	5 (4)	3 (7)	5 (4)	1 (2)
Oral candidiasis	6 (5)	0	5 (4)	5 (12)
Acute sinusitis	1 (< 1)	0	2 (2)	1 (2)
Urinary tract infection	3 (2)	0	2 (2)	2 (5)
Influenza	10 (8)	2 (5)	8 (6)	5 (12)
Gastroenteritis viral	0	1 (2)	1 (< 1)	2 (5)
Viral upper respiratory tract infection	1 (< 1)	1 (2)	3 (2)	0
Gastroenteritis	3 (2)	2 (5)	1 (< 1)	0
Injury, poisoning, procedural complications	13 (10)	2 (5)	8 (6)	7 (17)
Procedural pain	1 (< 1)	0	1 (< 1)	2 (5)
Investigations	2 (2)	3 (7)	2 (2)	2 (5)
Cortisol free urine decreased	0	1 (2)	0	2 (5)
Musculoskeletal and connective tissue disorders	13 (10)	2 (5)	13 (10)	5 (12)
Back pain	1 (< 1)	0	1 (< 1)	3 (7)
Arthralgia	0	2 (5)	5 (4)	1 (2)
Myalgia	4 (3)	0	0	0
Pain in extremity	2 (2)	0	3 (2)	0
Nervous system disorders	11 (9)	4 (10)	10 (8)	1 (2)
Headache	5 (4)	2 (5)	6 (5)	1 (2)

Adverse Events, n (%)	Fp MDPI 113 mcg b.i.d. (N = 127)	Fp HFA 110 mcg b.i.d. (N = 42)	Fp MDPI 232 mcg b.i.d. (N = 125)	Fp HFA 220 mcg b.i.d. (N = 41)
Respiratory, thoracic, and mediastinal disorders	35 (28)	9 (21)	31 (25)	7 (17)
Asthma	6 (5)	0	4 (3)	0
Oropharyngeal pain	13 (10)	5 (12)	6 (5)	1 (2)
Cough	10 (8)	3 (7)	13 (10)	4 (10)
Dyspnea	1 (< 1)	0	1 (< 1)	0
Rhinitis allergic	1 (< 1)	0	2 (2)	1 (2)
Sinus congestion	1 (< 1)	3 (7)	3 (2)	0
Respiratory tract congestion	1 (< 1)	3 (7)	0	0
Nasal congestion	2 (2)	0	3 (2)	2 (5)

b.i.d. = twice daily; FP MDPI = fluticasone propionate multidose dry powder inhaler.

Source: Clinical study reports.[8]

Serious Adverse Events

In the efficacy trials 301 and 30017, a total of six patients reported treatment-emergent SAEs, with a similar incidence observed among treatment groups (0% to 2%). Two patients, both treated with placebo, reported SAEs related to asthma considered by the investigators to be related to the study drug.

Table 34: Serious Adverse Events in the Efficacy Trials

SAEs, n (%)	Study 301			Study 30017		
	Placebo (N = 129)	Fp MDPI 55 mcg b.i.d. (N = 129)	Fp MDPI 113 mcg b.i.d. (N = 129)	Placebo (N = 144)	Fp MDPI 113 mcg b.i.d. (N = 145)	Fp MDPI 232 mcg b.i.d. (N = 146)
Any SAEs	2 (2)	0	1 (< 1)	1 (< 1)	1 (< 1)	1 (< 1)
GI disorders	0	0	0	NR	NR	NR
Pancreatitis	0	0	0	NR	NR	NR
General disorders and administration site conditions	NR	NR	NR	0	0	1(< 1)
Pyrexia	NR	NR	NR	0	0	1(< 1)
Hepatobiliary disorders	0	0	0	NR	NR	NR
Cholecystitis	0	0	0	NR	NR	NR
Cholelithiasis	0	0	0	NR	NR	NR
Neoplasms benign, malignant, and unspecified	0	0	1 (< 1)	0	0	0
Plasma cell myeloma	0	0	1 (< 1)	NR	NR	NR
Pregnancy, puerperium, and perinatal conditions	1 (< 1)	0	0	NR	NR	NR
Abortion spontaneous	1 (< 1)	0	0	NR	NR	NR
Nervous system disorders	NR	NR	NR	0	1(< 1)	0
Grand mal convulsion	NR	NR	NR	0	1(< 1)	0
RTM disorders	1 (< 1)	0	0	1 (< 1)	0	0
Asthma	1 (< 1)	0	0	1 (< 1)	0	0

FP MDPI = fluticasone propionate multidose dry powder inhaler; b.i.d. = twice daily; NR = not reported; RTM = respiratory, thoracic, and mediastinal; SAE= serious adverse events.

Source: Clinical study reports.[6,7]

In the long-term trial, safety Study 305, the frequency of SAEs was higher than that observed in the efficacy trials (5% to 7%), with similar incidences across treatment groups. Overall, 20 patients treated with either Fp MDPI or Fp HFA had one or more SAEs. As in the efficacy trials, asthma exacerbation was the most frequently reported SAE (3% to 5% in the Fp MDPI groups, and 0% in the Fp HFA group). One SAE was considered by the investigator to be related to study drug: moderate asthma for a patient who received Fp MDPI 113 mcg.

Table 35: Serious Adverse Events in the Safety Trial

SAEs, n (%)	Fp MDPI 113 mcg b.i.d. (N = 127)	Fp HFA 110 mcg b.i.d. (N = 42)	Fp MDPI 232 mcg b.i.d. (N = 125)	Fp HFA 220 mcg b.i.d. (N = 41)
At least 1 SAE	7 (6)	2 (5)	8 (6)	3 (7)
Cardiac disorders	0	0	1 (< 1)	1 (2)
Acute myocardial infarction	0	0	1 (< 1)	0
Atrial tachycardia	0	0	0	1 (2)
General disorders and administration site conditions	0	0	0	1 (2)
Device dislocation	0	0	0	1 (2)
Hepatobiliary disorders	1 (< 1)	0	0	0
Biliary colic	1 (< 1)	0	0	0
Cholelithiasis	1 (< 1)	0	0	0
Infections and infestations	0	0	1 (< 1)	1 (2)
Cellulitis	0	0	0	1 (2)
Lobar pneumonia	0	0	1 (< 1)	0
Injury, poisoning, and procedural complications	0	1 (2)	0	1 (2)
Fall	0	1 (2)	0	0
Hip fracture	0	1 (2)	0	0
Wound dehiscence	0	0	0	1 (2)
Pregnancy, puerperium, and perinatal conditions	0	0	2 (2)	0
Abortion spontaneous	0	0	1 (< 1)	0
Ectopic pregnancy	0	0	1 (< 1)	0
RTM disorders	6 (5)	1 (2)	5 (4)	0
Asthma	6 (5)	0	4 (3)	0
Pulmonary embolism	0	1 (2)	0	0
Pulmonary mass	0	0	1 (< 1)	0

FP MDPI = fluticasone propionate multidose dry powder inhaler; b.i.d. = twice daily; NR = not reported; RTM = respiratory, thoracic, and mediastinal; SAE = serious adverse events.

Source: Clinical study report.[8]

Withdrawal Due to Adverse Events

Withdrawal due to adverse events in these studies was rare (≤ 2% in active arms of the studies, and ≤ 5% in placebo arms of the studies). In the safety Study 305, four patients treated with Fp MDPI or Fp HFA withdrew because of AEs (asthma exacerbation, dysphonia, upper respiratory tract infection, and hypertension).

Table 36: Withdrawal Due to Adverse Events in the Safety Trial

WDAEs, n (%)	Fp MDPI 113 mcg b.i.d. (N = 127)	Fp HFA 110 mcg b.i.d. (N = 42)	Fp MDPI 232 mcg b.i.d. (N = 125)	Fp HFA 220 mcg b.i.d. (N = 41)
Any WDAE	2 (2)	1 (2)	0	1 (2)
Infections and infestations	0	1 (2)	0	0
URTIs	0	1 (2)	0	0
RTM disorders	2 (2)	0	0	0
Asthma	1 (< 1)	0	0	0
Dysphonia	1 (< 1)	0	0	0
Vascular disorders	0	0	0	1 (2)
Hypertension	0	0	0	1 (2)

b.i.d. = twice daily; CTD = connective tissue disorder; RTM = respiratory, thoracic, and mediastinal; URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse event.

Source: Clinical study report.[8]

In the two efficacy studies, a total of 23 patients were withdrawn from the study due to AEs, with a similar incidence observed among treatment groups (0% to 2%). Asthma was reported as an AE leading to withdrawal from the study by three patients who received placebo under alert criteria and withdrawn by investigators if it was deemed the patient's worsening asthma warranted withdrawal.

Bronchitis, cough, and dysphonia were reported as AEs leading to withdrawal from the study by two patients each. All other AEs leading to withdrawal occurred in one patient each. The AEs of lip swelling (one patient who received placebo); asthma (one patient who received placebo); dysphonia, muscle spasms, and anxiety (one patient who received Fp MDPI 55 mcg); and cough (one patient who received Fp MDPI 113 mcg) were considered treatment-related.

Table 37: Withdrawal Due to Adverse Events in the Efficacy Trials

WDAEs, n (%)	Study 301			Study 30017		
	Placebo (N = 129)	Fp MDPI 55 mcg b.i.d. (N = 129)	Fp MDPI 113 mcg b.i.d. (N = 129)	Placebo (N = 144)	Fp MDPI 113 mcg b.i.d. (N = 145)	Fp MDPI 232 mcg b.i.d. (N = 146)
Any WDAE	6 (5)	1 (< 1)	2 (2)	2 (1)	2 (1)	0
Cardiac disorders	0	0	0	NR	NR	NR
Tachycardia	0	0	0	NR	NR	NR
Gastrointestinal disorders	1 (< 1)	0	0	NR	NR	NR
Lip swelling	1 (< 1)	0	0	NR	NR	NR
Infections and infestations	1 (< 1)	0	0	1 (< 1)	1 (< 1)	0
Nasopharyngitis	1 (< 1)	0	0	NR	NR	NR
URTIs	0	0	0	NR	NR	NR
Bronchitis	NR	NR	NR	1 (< 1)	1 (< 1)	0
Pneumonia	NR	NR	NR	0	0	0
Musculoskeletal and CTD	0	1 (< 1)	0	NR	NR	NR
Back pain	0	0	0	NR	NR	NR
Muscle spasms	0	1 (< 1)	0	NR	NR	NR
Neoplasms benign, malignant, and unspecified	0	0	1 (< 1)	NR	NR	NR

WDAEs, n (%)	Study 301			Study 30017		
	Placebo (N = 129)	Fp MDPI 55 mcg b.i.d. (N = 129)	Fp MDPI 113 mcg b.i.d. (N = 129)	Placebo (N = 144)	Fp MDPI 113 mcg b.i.d. (N = 145)	Fp MDPI 232 mcg b.i.d. (N = 146)
Plasma cell myeloma	0	0	1 (< 1)	NR	NR	NR
Nervous system disorders	NR	NR	NR	0	1 (< 1)	0
Grand mal convulsion	NR	NR	NR	0	1 (< 1)	0
Pregnancy, puerperium, and perinatal conditions	1 (< 1)	0	0	NR	NR	NR
Abortion spontaneous	1 (< 1)	0	0	NR	NR	NR
Psychiatric disorders	0	1 (< 1)	0	NR	NR	NR
Anxiety	0	1 (< 1)	0	NR	NR	NR
RTM disorders	3 (2)	1 (< 1)	1 (< 1)	1 (< 1)	0	0
Asthma	2 (2)	0	0	1 (< 1)	0	0
Cough	1 (< 1)	0	1 (< 1)	NR	NR	NR
Dysphonia	1 (< 1)	1 (< 1)	0	NR	NR	NR

b.i.d. = twice daily; CTD = connective tissue disorder; NR = not reported; RTM = respiratory, thoracic, and mediastinal; URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse event.

Source: Clinical study report.[6,7]

Mortality

There were no deaths in either of the placebo or Fp MDPI arms of the included studies.

Discussion

Summary of Available Evidence

Three multi-centre, parallel-group RCTs met criteria for inclusion in the systematic review. Two of these included trials were double-blind, placebo-controlled, efficacy trials; one trial was an active-controlled, open-label safety trial. The included trials evaluated Fp MDPI by comparing efficacy with Fp HFA or placebo. Two trials evaluated the superiority of Fp MDPI at 55 mcg, 113 mcg, and 232 mcg twice daily compared with placebo. The third trial was primarily a safety study, but also evaluated the noninferiority of the pooled arms of Fp MDPI 113 mcg and 232 mcg twice daily compared with the pooled arms of Flovent 110 mcg and 220 mcg twice daily with respect to both efficacy and safety. All trials included patients at least 12 years of age, with prior treatment of ICS or ICS/LABA at a qualifying dosage and a diagnosis of asthma present for at least three months with no exacerbations or changes to medications for at least one month before consent being given to participate in the trial.

In both 12-week efficacy trials, there were a higher number of premature withdrawals in the placebo arms than in the Fp MDPI arms, which were generally due to worsening asthma, and were subsequently imputed. While the validity of the conclusions about evidence of efficacy made by the primary imputation methods were confirmed with tipping point sensitivity analyses, it remains to be seen whether the estimated effects are sufficiently reliable. In addition, the potential for unblinding within patients in the placebo arms of these studies cannot be ruled out. The only head-to-head comparative evidence was provided by the safety study, Study 305, versus Fp HFA. Therefore, there is a gap in understanding the comparative dosing, efficacy, and safety versus other ICS products.

The age of trial patients ranged from 12.0 to 79.0 years, with a slightly higher proportion of females. The majority of study patients had, on average, a history of asthma for 15 years or longer. The mean pre-bronchodilator FEV_1, at screening, ranged from 2.069 L to 2.700 L. According the clinical expert consulted in this review, the patients recruited in the two efficacy trials appeared to have suboptimal control of their asthma relative to the Canadian population at the point of randomization, which may affect its application.

Three additional studies, one phase I pharmacokinetic study and two phase II dose-ranging studies, were summarized in Appendix 8 as supplemental information.

Interpretation of Results

Efficacy

With respect to lung function, both efficacy studies were able to demonstrate superiority of Fp MDPI to placebo in a change from baseline in in trough FEV_1 at week 12. Both of these studies evaluated the 113 mcg dose, and one study each evaluated the 55 mcg and 232 mcg doses. In Study 301, the difference from placebo in trough FEV_1 for Fp MDPI 55 mcg twice daily was 0.119 L (P = 0.0132) and for Fp MDPI 113 mcg twice daily was 0.151 L (P = 0.0017). In Study 30017, the difference from placebo in trough FEV_1 for Fp MDPI 113 mcg twice daily 0.123 L (P = 0.0047) and for 232 mcg twice-daily was 0.183 L (P < 0.0001). Little evidence is available on the MCID for FEV_1, yet the between-group differences were below the minimum patient perceivable improvement values reported in the literature (0.23 L)[31] and below the MCID suggested by the Health Canada reviewer (0.20 L).[2] The Health Canada reviewer noted that the 0.20 L MCID may be more applicable for ICS (or ICS/LABA) treatment-naive patients. The Health Canada reviewer further indicated that the changes were considered “clinically acceptable” as compared with placebo. Nevertheless, if one was to accept the between-group differences in change from baseline in trough FEV_1 as clinically significant, this represents improvement versus placebo in a chronic condition for which ICS is the recommended mainstay of therapy, over a follow-up duration of 12 weeks.

The third, safety, open-label trial clearly stated that it was first and foremost a safety study; however, it had 90% power for demonstrating noninferiority of Fp MDPI to Fp HFA with the medium-, and high-strength data combined, for change from baseline in trough FEV_1 over the 26-week treatment period, with a noninferiority margin pre-specified as –0.125 L. Comparable results were observed for the pooled analysis of Fp MDPI and Fp HFA groups. The change from baseline over the 26 week period yielded baseline difference in trough FEV_1 of Fp MDPI from Fp HFA groups of –0.002 L (95% CI, -0.068 to 0.065). Therefore, the treatment effect and lower limit of the 95% confidence interval exceeded the –0.125 L noninferiority margin for FEV_1.

The change in FEV_1 from baseline for the safety Study 305 was lower than those observed in the efficacy studies (301 and 30017). The clinical expert consulted for this review believed that this may be due to the fact that during the run-in period of the efficacy trials, patients were switched from their current asthma medication and placed on a low-dose ICS treatment.

Health-related quality of life (HRQoL) measures were included in this systematic review to provide the patient perspective of treatment and because HRQoL was identified as an outcome that was important to patients, as reported in the patient input section (Appendix 1). Results with respect to AQLQ(S) were inconsistent. For Study 301, the mean AQLQ(S)

score was found to improve from baseline as compared with placebo; however, because hierarchical testing failed at a higher level comparison before this outcome, the results were considered hypothesis generating. In Study 30017, the treatment arm Fp MDPI 113 mcg was found not to statistically significantly improve AQLQ(S) scores at the end of the 12-week treatment period versus placebo (*P* = 0.1962). There was a statistically significant improvement observed at the end of 12 weeks in the Fp MDPI 232 mcg treatment arm for this outcome (LS mean change versus placebo, 0.216; 95% CI, 0.017 to 0.415; *P* = 0.0334); however, this difference did not reach the ≥ 0.5 MCID threshold to be considered clinically significant. According to the clinical expert involved in this review, the 12-week duration of treatment was likely insufficient to achieve clinically meaningful change from baseline for this outcome.

Asthma exacerbations are recognized as important outcomes of the disease and were identified in the patient input. The frequency of asthma exacerbations was low in general in the efficacy studies. A statistically significant difference in favour of Fp MDPI 113 mcg and 232 mcg treatment groups as compared with placebo was shown in the analysis of time to patients withdrawal due to asthma exacerbation. In the 26-week safety study, the efficacy analysis of exacerbations focused on the time to first severe asthma exacerbation. Severe asthma exacerbations occurred at a numerically higher frequency in the Fp MDPI groups than in the Fp HFA groups, although the differences were not statistically significant. The clinical importance of the exacerbation results are highly uncertain. None of the studies were designed to assess exacerbations as a primary outcome, despite prevention of asthma exacerbations being recognized by the ATS/ERS Task Force on clinical asthma trials and clinical practice as "as an important component of establishing ideal asthma control" and "exacerbations are the most important outcome, because they constitute the greatest risk to patients, are a cause of anxiety to patients and their families, result in the greatest stress on health care providers, and generate the greatest cost to the health care system."[34] All three included studies were relatively too short in duration to adequately evaluate the rates of asthma exacerbations.[35] Also, comparing exacerbation rates across studies is difficult given the variation in populations included and the definitions for exacerbations. As well, in Study 305 there was no collection of baseline asthma exacerbation rates within the treatment groups, so it is unknown whether there was a difference between patients in these groups at baseline. It is also worth noting that in this study there was a difference in sample size between Fp MDPI (N = 243) and Fp HFA (N = 83); therefore, this imbalance may have been due to chance.

Results for change from baseline in the weekly average of total daily asthma symptom scores over weeks 1 to 12 in the efficacy studies showed an overall improvement in scores over time compared with placebo. In Study 301, the Fp MDPI 113 mcg arm had a significant reduction in asthma symptoms scores relative to placebo (*P* = 0.0002), while significant differences in the Fp MDPI 55 mcg arm could not be concluded in accordance with the fixed-sequence testing procedure, due to findings for the change from baseline in the weekly average of the daily trough morning PEF. For Study 30017, both the Fp MDPI 113 mcg group and the Fp MDPI 232 mcg had a significantly lower total daily asthma symptom score in the weekly average from baseline than those in the placebo group. The magnitude of improvement in mean change from baseline at each week increased over time in all active treatment groups. In the long-term Study 305, the LS mean changes from baseline in asthma symptom scores were similar between the Fp MDPI and Fp HFA groups at both strengths over the 26-week treatment period.

Results for the change from baseline in the weekly average of the total daily (24-hour) use of salbutamol inhalation aerosol, number and percentage of symptom-free days, and asthma-control (24-hour) periods over weeks 1 to 12 varied between studies. In Study 301, there were no significant differences observed in the percentage of rescue-free (24-hour) periods in either of the Fp MDPI groups compared with the placebo group. In Study 30017 however, there was a significant difference for this outcome observed for both the Fp MDPI 113 mcg group ($P = 0.0002$) and the Fp MDPI 232 mcg group ($P < 0.0001$). Similarly in Study 301 there were no significant differences observed in either of the Fp MDPI groups ($P = 0.1060$ in the Fp MDPI 55 mcg group, and $P = 0.0596$ in the Fp MDPI 113 mcg group) compared with the placebo group, while in Study 30017, a significant difference was observed for this outcome in the Fp MDPI 113 mcg group ($P = 0.0047$) and the Fp MDPI 232 mcg group ($P = 0.0013$). Lastly for the outcome of changes from baseline in asthma control (24-hour) periods (defined as 24-hour periods with asthma symptom scores of zero and no rescue medication usage) over 12 weeks, Study 301 did approach statistical significance in the 55 mcg arm when compared with placebo ($P = 0.0461$); however, the difference was not significant when comparing the Fp MDPI 113 mcg arm with placebo ($P = 0.1309$). In Study 30017, changes from baseline were statistically significant in both Fp MDPI 113 mcg ($P = 0.0046$) and Fp MDPI 232 mcg ($P = 0.0030$) treatment arms compared with placebo.

In the long-term safety Study 305, changes from baseline in the weekly average of total daily (24 hour) use of albuterol/salbutamol inhalation aerosol and percentages of symptom-free (24-hour) days were measured. Mean baseline percentages for these values in this study (58.2% to 65.5%) varied in comparison to studies 301 and 30017 (33.0% to 44.5%). This is likely because the run-in period for these studies differed in that patients in the safety study did not discontinue their prior ICS or ICS/LABA medication during this period. There were no statistical differences observed in the numbers and percentages of symptom-free days, as well as percentage of rescue-free 24-hour periods between the Fp MDPI and Fp HFA groups, although this study was not powered to detect a difference in these outcomes. Further, this was an open-label study and the potential for reporting bias exists.

The long-term safety study, Study 305, examined resource consumption between treatment arms, and, overall the reported average amount of health care resource consumption was high across different areas of health care. Over the course of this 26-week study, a total of 28% (91 of 326) of patients reported an unscheduled or outpatient visit, 14% (45 of 326) of patients reported an emergency department or urgent care visit, and 3% (9 of 326) of patients reported a hospital visit. Concerns were raised by the clinical expert involved in this review about these results as it is much higher than the average of those observed among asthma patients in Canada, based on his experience.

[redacted] which included two phase II trials (Study 201 and Study 202), along with the two pivotal phase III efficacy trials (studies 301 and 30017) and one long-term safety trial (Study 305).[2,5] The phase II trials were dose-ranging trials designed to determine superiority in efficacy of Fp MDPI compared with placebo for the change in trough FEV_1 after 12 weeks across a range of doses of Fp MDPI. Both studies included an active-control Flovent Diskus arm.[16,17] Both trials, as well as one phase I trial evaluating the pharmacokinetics of Fp MDPI and Flovent Diskus, are summarized in Appendix 8. The phase I trial indicated that after administration of high-strength doses of Fp MDPI and Flovent Diskus,[4,7] the systemic exposure of fluticasone propionate was approximately 20%

to 30% lower in the Fp MDPI inhaler. Studies 201 and 202 suggested that there were no statistically significant differences observed between the Fp MDPI doses currently marketed and Flovent Diskus 100 mcg and 250 mcg for change in trough FEV_1 over 12 weeks, but this does not necessarily indicate equivalence or noninferiority between these two products.[4,17] [redacted] however, a dose-response study, as well as two pivotal phase III efficacy and safety studies and one long-term safety study, are required along with chemistry and manufacturing data. Health Canada noted that the Fp MDPI phase III studies were considered pivotal for its review and that the phase II studies were supportive. As the phase III studies were not designed with the primary goal of comparing Fp MDPI with an active-control group to establish efficacy and safety between Fp MDPI and Flovent Diskus, the phase II studies provide data in this regard.[2,5] However, as noted, the lack of a finding of statistical difference does not translate to equivalence or noninferiority. Furthermore, there were important limitations with the studies, particularly the high rates of premature discontinuation that were likely systematic and not random. Therefore, there remains a degree of uncertainty regarding the dose equivalency and efficacy equivalency of Fp MDPI compared with Flovent Diskus. Notably, FDA reanalysis of the primary outcome comparisons in Study 201 supported the main results. As well, the product monograph for Fp MDPI recommends starting dosages for patients based on the patients' asthma severity, and if the patient's current ICS dose is low, medium, or high they may switch to the respective starting doses, which are the low (55 mcg), medium (113 mcg), and high (232 mcg) doses of Fp MDPI. Health Canada stated that this was based on the inclusion criteria and the patient population in the pivotal phase III clinical trials; i.e., the ICS treatment dose of patients pre-randomization (low, medium, or high) directed to the dose (Fp MDPI 55 mcg, 113 mcg, or 232 mcg) they were randomized to in the phase III clinical trials (see Table 7).

In the absence of phase III head-to-head trial data for Fp MDPI compared with other combination therapies, and given that a limited number of outcomes were studied in the manufacturer-sponsored studies, an indirect treatment comparison was conducted based on a systematic review of RCTs to compare the efficacy of Fp MDPI against other similar treatments currently available. Information for the indirect comparison is summarized in Appendix 7. The primary outcomes in this study were FEV_1, FEV_1 area under the curve, and asthma exacerbations. [redacted] It is worth noting, however, that longer-term data were not required for regulatory approval and, in general, a simpler data base was required for Fp MDPI.

Harms

The incidence of AEs in patients treated with Fp MDPI was similar across studies. SAEs were rare (< 7% across studies), and did not suggest any association with specific treatments. There were no deaths reported across any of the three studies in arms which are relevant to this report.

The most common AEs reported in any treatment arm and across all studies were nasopharyngitis, URTIs, oral candidiasis, headache, and cough. With respect to oral candidiasis, there was a slightly higher incidence reported in the Fp MDPI 232 mcg arm (4%) and the Fp HFA 220 mcg arm (12%). The clinical expert involved in this study believed that this is effect is typically dose-related.

Safety assessments in the indirect treatment comparison were limited due to variability in follow-up time, heterogeneity of reporting across studies, and rarity of events. Overall, there were no signals of potential safety issues presented in the analysis; however, there was similarly a lack of evidence to support any inferences of superiority compared with other available products.

Potential Place in Therapy[1]

Since the introduction of effective controller medications such as ICS asthma mortality has decreased.[36] Asthma control in Canada, however, continues to be suboptimal. The Public Health Agency of Canada, although not current, describes asthma prevalence in those 12 years and older of 8.4%. Only 34.4% of Canadians were classified as having well-controlled asthma and 11.1% had at least one visit to a hospital emergency in the previous year. Almost 40% of those surveyed did not understand the reason behind taking their medications; that is, the medications were to be used as a preventive mechanism for acute symptom control. Asthma control in Canada has not changed appreciably over a 10-year span despite increased numbers of ICS available for therapy.[37] Therefore, it is unlikely that one more ICS will appreciably improve asthma care in Canada. It is possible that less expensive ICS medications would improve accessibility of therapy for lower income Canadians. However, the interactions of socioeconomic status and asthma control are complex and include education level, ambient tobacco smoke exposure, and psychosocial stress.[15] Cost of medications is only one factor.

In general, ICS monotherapy is the first step in treating patients with persistent asthma symptoms. This drug is therefore aimed at patients with mild asthma. Patients who gain control of asthma symptoms and stabilize lung function do not require additional drug therapy. The only tests required to identify these patients would be spirometry or bronchoprovocation testing to confirm the diagnosis of asthma. Subsequent evaluation would include assessment of asthma control using questionnaire(s) and assessment of airflow obstruction using occasional spirometric testing or PEF monitoring.

[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.

Conclusions

Three parallel-group randomized controlled trials that recruited patients 12 years and older with asthma, who were inadequately controlled on ICS were included in studies in which two different doses of Fp MDPI were compared against either placebo or Fp HFA for a minimum of 12 weeks and up to 26 weeks. There is limited comparative evidence for the use of Fp MDPI versus alternative ICS therapies. Consequently, no concrete conclusions can be drawn with respect to the comparative effects of Fp MDPI on asthma exacerbations.

Supportive data from two phase II dose-ranging studies suggested no statistically significant differences between Fp MDPI and Flovent Diskus for the change in trough FEV_1 over 12 weeks of treatment; however, this does not necessarily mean the Fp products are equivalent or noninferior to each other. Fp MDPI was found to be significantly superior to placebo with respect to pulmonary function. Results from the phase III efficacy studies suggest that compared with placebo, Fp MDPI 55 mcg, 113 mcg, and 232 mcg improved FEV_1 and increased the number of days without asthma symptoms through 12 weeks. Fp MDPI may improve quality of life relative to placebo; however, the effect was inconsistent across studies. No rigorous assessment of patient preferences regarding the Fp MDPI inhaler in comparison with other available devices in this patient population was identified. Studies were limited by their duration (12 to 26 weeks) because of the reduced evidence requirements for this second entry product. Nevertheless, considering the chronic use of ICS in patients with asthma, the submitted direct and indirect data do not provide evidence for the longer-term effects of FP MDPI; longer-term comparative studies would be useful to elucidate the efficacy and harms of Fp MDPI beyond 26 weeks of exposure.

Appendix 1: Patient Input Summary

1. Brief Description of Patient Groups Supplying Input

Two patient groups, Asthma Canada and The Lung Association-Ontario, provided input for this summary.

Asthma Canada is a nationally registered charitable organization that provides support to all Canadians affected by asthma, with the aim to advocate for people living with asthma and associated allergies. The Asthma Canada Member Alliance (ACMA) is the patient arm and voice of Asthma Canada. Created in 2007, it serves in an advisory capacity with active volunteers to further the purpose of Asthma Canada's programs and initiatives, and to increase awareness and education about asthma within Canada. Asthma Canada has received funding from Teva Canada in the past two years totalling an excess of $50,000, and requested and received a medical briefing from Teva Canada regarding fluticasone propionate. Asthma Canada also received funding from GlaxoSmithKline, Astra Zeneca, and Novartis in the past two years totalling an excess of $50,000.

The Lung Association-Ontario (TLA-O) is a registered charity that assists and empowers people living with or caring for others with lung disease, including asthma. It is part of a federated model and works with nine other provincial lung associations and the Canadian Lung Association. The Association provides programs and services to patients and health care providers, invests in lung research and advocates for lung health policies. TLA-O has received funding between $10,000 and $50,000 from Teva Canada, as well as financial support from GlaxoSmithKline, Astra Zeneca, Boehringer Ingelheim, Pfizer, Sanofi Pasteur, Merck Canada, and Novartis in the past two years totalling an excess of $50,000.

2. Condition-Related Information

The information provided in the submission from Asthma Canada was a summary of:

- an Asthma Canada online survey sent to ACMA members with respect to the use of medications, daily management of asthma and the impact of asthma on quality of life
- information from a study conducted by the Asthma Society of Canada in 2014, entitled "Severe Asthma: The Canadian Patient Journey"
- peer-reviewed studies which were sourced for the purposes of this submission
- a requested medical briefing provided by Teva Canada. The online survey was sent to ACMA members in July 2017 and 88 responses were received. A total 85% of respondents had received a diagnosis of asthma and 13% identified themselves as caregivers of an individual with asthma.

The information provided in the submission from TLA-O was obtained from:

- two phone interviews (completed in October 2017)
- five online surveys (completed in 2016)
- input from a certified respiratory educator. All patient reports were from individuals living in Ontario, Canada, with asthma.

With regard to the included phone interviews, one was with a woman in her fifties who's had chronic severe asthma for 22 years, and the other was a woman in her thirties who has had asthma for ten years. Both patients indicated their asthma symptoms were particularly bad this year. Characteristics of the people responding to the online surveys were not reported.

Patients living with asthma experience a wide range of symptoms relating to the severity and control of their disease, including shortness of breath, chronic cough, wheezing, and nighttime waking. The patient groups reported that asthma limits physical and social activities, and that patients experience increased emergency room visits and hospitalizations. As a result, staying active on a regular basis can be challenging for some, and depression and anxiety around this condition can develop. TLA-O also highlighted that fatigue, difficulty fighting infections, and management of weight loss were important aspects to control for people with asthma.

Asthma Canada highlighted the burden of asthma on caregivers, who may experience an emotional burden (e.g., fear, stress, anxiety) and/or financial impact (e.g., time off work) as a result of having to care for a person with severe asthma. Interruptions to sleep and other aspects of a caregiver's daily life may also be adversely affected.

3. Current Therapy-Related Information

Both patient groups reported current treatment options for the management of asthma symptoms include a combination of long-term controller medications (i.e., inhaled corticosteroids, long-acting bronchodilators, and leukotriene receptor antagonists) and/or fast-acting reliever medications for acute symptoms (i.e., short-acting beta-2 agonist inhalers). It was reported that patients also received systemic corticosteroids and biologics therapies (anti-IgE and anti-IL5 drugs). Asthma Canada noted that current treatments are only somewhat effective because patients reported feeling that they do not have control of their disease. TLA-O noted that current therapies do provide some relief from symptoms, including: fatigue, shortness of breath, cough, low energy, poor appetite, and the inability to fight infection. They, however, report several adverse events associated with current treatments, including hoarse voice, increased mucus, low energy/fatigue, appetite loss, and an impact on mood. Both patients groups also acknowledged the cost burden of current treatments, as well as the intensive time requirements with regards to medical appointments.

Asthma Canada highlighted an unmet need with existing asthma medication. In particular, there is an importance for medicines that will improve symptom control, halt the progression of asthma, as well as prevent (or reduce) associated hospitalizations. It reported the need of therapies that will help patients to "live life to the fullest every day without fear of an exacerbation." Patients interviewed by TLA-O similarly re-iterated that an ideal treatment would improve quality of life and improve lung function. Additional outcomes they wished treatment could address include greater assistance with asthma management such as reducing shortness of breath, coughing and fatigue; improving energy levels and appetite; and, increasing one's ability to fight infections.

4. Expectations About the Drug Being Reviewed

No patients within either submission were reported to have used Aermony RespiClick. No patients within the TLA-O submission reported to have used fluticasone propionate.

ACMA survey participants were asked for their impressions on the potential availability of a "controller inhaler that follows a simple, three-step process that administers a consistent low dose, and includes active metering, such as fluticasone propionate." Responses from 58 of 76 (76%) survey participants indicated that such a controller inhaler would be expected to improve the lives for people with asthma. Seventy per cent of respondents said they would be more likely to take their medication regularly if it had these characteristics. One out of five respondents (20%) said they would and 34 respondents (45%) said they were unsure when asked if they would be willing to experience adverse events from a new controller inhaler.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE ALL 1946 to present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	March 5, 2018
Alerts:	Monthly search updates until July 18, 2018.
Study Types:	No search filters were applied
Limits:	No language or data limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
.dv	Device trade name
.dm	Device manufacturer
medall	Ovid database code; MEDLINE ALL 1946 to present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	(respiclick* or armonair* or aermony*).ti,ab,kf,ot,hw,rn,nm.
2	exp Fluticasone/
3	(2GMZ0LF5W or CUT2W21N7U).rn,nm.
4	fluticasone*.ti,ab,kf,ot,hw,rn,nm.
5	or/2-4
6	Dry Powder Inhalers/
7	(dry powder inhal* or MDPI or MDPIs or DPI or DPIs or Teva).ti,ab,kf.
8	or/6-7

MULTI-DATABASE STRATEGY	
9	exp Asthma/
10	(asthma* or antiasthma* or wheez*).ti,ab,kf.
11	(bronchospas* or bronchiospas* or (bronch* adj2 spas*)).ti,ab,kf.
12	or/9-11
13	5 and 8 and 12
14	1 or 13
15	14 use medall
16	(respiclick* or armonair* or aermony*).ti,ab,kw,dv.
17	*fluticasone propionate/
18	fluticasone*.ti,ab,kw,dv.
19	or/17-18
20	dry powder inhaler/
21	(dry powder inhal* or MDPI or MDPIs or DPI or DPIs or Teva).ti,ab,kw,dv,dm.
22	or/20-21
23	exp Asthma/
24	(asthma* or antiasthma* or wheez*).ti,ab,kw.
25	(bronchospas* or bronchiospas* or (bronch* adj2 spas*)).ti,ab,kw.
26	or/23-25
27	19 and 22 and 26
28	16 or 27
29	28 use oemezd
30	conference abstract.pt.
31	29 not 30
32	15 or 31
33	remove duplicates from 32

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. 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:	February to March 2018
Keywords:	Aermony RespiClick (fluticasone propionate), 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 searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

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

Appendix 3: Excluded Studies

Table 38: Excluded Studies

Reference	Reason for Exclusion
[32]	Phase II study
[38]	Phase II study
[39]	Review Article
[40]	Review Article

Appendix 4: Detailed Outcome Data

Table 39: Comparisons Between FS MDPI Dosage Strengths to Fp MDPI Dosage Strengths for Primary and Secondary Outcomes in Study 301

Comparison	Difference (CI)	*P* Value
Change in trough FEV_1 at 12 weeks		
FS MDPI 113 mcg/14 mcg b.i.d. vs. Fp MDPI 113 mcg b.i.d.	0.152 (0.066 to 0.237)	0.0005
FS MDPI 232 mcg/14 mcg b.i.d. vs. Fp MDPI 232 mcg b.i.d.	0.092 (0.006 to 0.177)	0.0356
FS MDPI 232 mcg/14 mcg b.i.d. vs. Fp MDPI 232 mcg b.i.d.	0.093 (0.009 to 0.178)	0.0309
Standardized baseline-adjusted FEV_1 AUEC0-12hr (L)		
FS MDPI 113 mcg/14 mcg b.i.d. vs. Fp MDPI 113 mcg b.i.d.	0.182 (0.074 to 0.291)	0.0010
FS MDPI 232 mcg/14 mcg b.i.d. vs. Fp MDPI 232 mcg b.i.d.	0.175 (0.066 to 0.284)	0.0017
FS MDPI 232 mcg/14 mcg b.i.d. vs. Fp MDPI 232 mcg b.i.d.	0.179 (0.074 to 0.285)	0.0009
Change in weekly average of the total daily asthma symptom scores		
FS MDPI 113 mcg/14 mcg b.i.d. vs. Fp MDPI 113 mcg b.i.d.	–0.082 (–0.174 to 0.010)	0.0818
FS MDPI 232 mcg/14 mcg b.i.d. vs. Fp MDPI 232 mcg b.i.d.	–0.121 (–0.213 to –0.030)	0.0094
FS MDPI 232 mcg/14 mcg b.i.d. vs. Fp MDPI 232 mcg b.i.d.	–0.149 (–0.239 to –0.058)	0.0014
Change in weekly average of the total daily use of albuterol/salbutamol		
FS MDPI 113 mcg/14 mcg b.i.d. vs. Fp MDPI 113 mcg b.i.d.	–0.382 (–0.681 to –0.083)	
FS MDPI 232 mcg/14 mcg b.i.d. vs. Fp MDPI 232 mcg b.i.d.	–0.287 (–0.584 to 0.011)	0.0588
FS MDPI 232 mcg/14 mcg b.i.d. vs. Fp MDPI 232 mcg b.i.d.	–0.364 (–0.659 to –0.068)	0.0160
Change in weekly average of the total daily use of albuterol/salbutamol		
FS MDPI 113 mcg/14 mcg b.i.d. vs. Fp MDPI 113 mcg b.i.d.	0.251 (0.065 to 0.437)	0.0083
FS MDPI 232 mcg/14 mcg b.i.d. vs. Fp MDPI 232 mcg b.i.d.	0.166 (–0.020 to 0.353)	0.0802
FS MDPI 232 mcg/14 mcg b.i.d. vs. Fp MDPI 232 mcg b.i.d.	0.117 (–0.072 to 0.306)	0.2258

b.i.d. = twice daily; CI = confidence intervals; Fp MDPI = fluticasone propionate multidose dry powder inhaler; FEV_1 = forced expiratory volume in one second; FS MDPI = fluticasone propionate/salmeterol xinafoate multidose dry powder inhaler; mcg = microgram.

Source: Clinical study report.[6]

Table 40: Comparisons Between FS MDPI Dosage Strengths to Fp MDPI Dosage Strengths for Primary and Secondary Outcomes in Study 30017

Comparison	Difference (CI)	*P* Value
Change in trough FEV_1 at 12 weeks		
FS MDPI 55 mcg/14 mcg b.i.d. vs. Fp MDPI 55 mcg b.i.d.	0.147 (0.053 to 0.242)	0.0022
FS MDPI 55 mcg/14 mcg b.i.d. vs. Fp MDPI 113 mcg b.i.d.	0.115 (0.021 to 0.210)	0.0166
FS MDPI 113 mcg/14 mcg b.i.d. vs. Fp MDPI 113 mcg b.i.d.	0.111 (0.017 to 0.206)	0.0202
Standardized baseline-adjusted FEV_1 AUEC0-12hr (L)		
FS MDPI 55 mcg/14 mcg b.i.d. vs. Fp MDPI 55 mcg b.i.d.	0.131 (0.011 to 0.250)	0.0322
FS MDPI 55 mcg/14 mcg b.i.d. vs. Fp MDPI 113 mcg b.i.d.	0.145 (0.028 to 0.261)	0.0151
FS MDPI 113 mcg/14 mcg b.i.d. vs. Fp MDPI 113 mcg b.i.d.	0.154 (0.041 to 0.267)	0.0076
Change in weekly average of the total daily asthma symptom scores		
FS MDPI 55 mcg/14 mcg b.i.d. vs. Fp MDPI 55 mcg b.i.d.	–0.051 (–0.136 to 0.035)	0.2438
FS MDPI 55 mcg/14 mcg b.i.d. vs. Fp MDPI 113 mcg b.i.d.	–0.029 (–0.114 to 0.057)	0.5095

Comparison	Difference (CI)	*P* Value
FS MDPI 113 mcg/14 mcg b.i.d. vs. Fp MDPI 113 mcg b.i.d.	–0.064 (–0.150 to 0.021)	0.1381
Change in weekly average of the total daily use of albuterol/salbutamol		
FS MDPI 55 mcg/14 mcg b.i.d. vs. Fp MDPI 55 mcg b.i.d.	–0.239 (–0.492 to 0.014)	0.0640
FS MDPI 55 mcg/14 mcg b.i.d. vs. Fp MDPI 113 mcg b.i.d.	–0.241 (–0.494 to 0.013)	0.0626
FS MDPI 113 mcg/14 mcg b.i.d. vs. Fp MDPI 113 mcg b.i.d.	–0.212 (–0.465 to 0.042)	0.1014
Change in weekly average of the total daily use of albuterol/salbutamol		
FS MDPI 55 mcg/14 mcg b.i.d. vs. Fp MDPI 55 mcg b.i.d.	–0.023 (–0.223 to 0.177)	0.8216
FS MDPI 55 mcg/14 mcg b.i.d. vs. Fp MDPI 113 mcg b.i.d.	–0.071 (–0.275 to 0.133	0.4934
FS MDPI 113 mcg/14 mcg b.i.d. vs. Fp MDPI 113 mcg b.i.d.	0.172 (–0.028 to 0.372)	0.0913

b.i.d. = twice daily; CI = confidence intervals; Fp MDPI = fluticasone propionate multidose dry powder inhaler; FEV_1 = forced expiratory volume in one second; FS MDPI = fluticasone propionate/salmeterol xinafoate multidose dry powder inhaler; mcg = microgram; vs. = versus.

Source: Clinical study report.[7]

Table 41: Analysis of Change from Baseline in Trough FEV_1 (L) Over 26-Week Treatment Period for Study 305 in Individual Dosage Arms

Variable	Medium-Dose Strength		High-Dose Strength	
	Fp MDPI 113 mcg b.i.d. (N = 123)	Fp HFA 110 mcg b.i.d. (N = 42)	Fp MDPI 232 mcg b.i.d. (N = 120)	Fp HFA 220 mcg b.i.d. (N = 41)
LS mean (SE)	0.062 (0.0243)	0.053 (0.0415)	0.077 (0.0246)	0.090 (0.0415)
95% CI	(0.015 to 0.110)	(–0.029 to 0.135)	(0.028 to 0.125)	(0.008 to 0.171)
Comparison of Fp HFA (Fp MDPI – Fp HFA)				
Difference of LS mean (SE)	0.009 (0.0476)		–0.013 (0.0479)	
95% CI	(–0.084 to 0.103)		(–0.107 to 0.081)	
P value	0.8451		0.7877	

b.i.d. = twice daily; CI = confidence intervals; FEV_1 = forced expiratory volume in one second; Fp MDPI = fluticasone propionate multidose dry powder inhaler; Fp HFA = fluticasone propionate hydrofluoroalkane; LS = least squares; mcg = microgram; SE = standard error.

Source: Clinical study report.[8]

Appendix 5: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- Asthma Control Test (ACT)
- Asthma Quality of Life Questionnaire for 12 years and older (AQLQ[S]12+)
- Total Daily Asthma Symptom Score.

Findings

The above outcome measures are briefly summarized in Table 42.

Table 42: Validity and MCID of Outcome Measures

Instrument	Type	Evidence of Validity	MCID (or Similar Parameter)	References
ACT	ACT is a patient-reported tool to assess asthma control among adolescents and adults, i.e., ≥12 years. It consists of five items relating to different aspects of asthma control that patients are asked to recall from the previous four weeks. Each item is scored on a five-point scale, which ranges from one to five, with greater scores indicating better asthma control. Scores from individual items are summed to produce an overall score ranging from 5 to 25.	Yes	A difference of 3.09 (1.06 to 5.28) points was deemed clnically meaningful in an adults.	Schatz 2009[41]
AQLQ(S)12+	AQLQ(S)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 four domains: symptoms; activity limitations; emotional function; and environmental stimuli. Each question is scored on a 7-point Likert scale, which ranges from 7 (no impairment) to 1 (severe impairment). The overall score is calculated as the mean of all questions, and the four domain scores are the means of the scores to the questions in the respective domains.	Yes	Not formally validated, but a difference of 0.5 has been considered clinically important, as per extensive validation of the AQLQ(S) in adults.	None
Total Daily Asthma Symptom Score	The total daily asthma symptom score is a patient-reported outcome concerning the occurrence of asthma symptoms and their effect on a patient's daily activities and sleep. It is composed of two parts: daytime (five items) and nighttime (four items), both scored ordinally. Higher scores indicate more severe symptoms. Daytime and nighttime scores are averaged for a total daily asthma symptom score.	No	Not identified	None

ACT = Asthma Control Test; AQLQ(S)12+ = Asthma Quality of Life Questionnaire With Standardized Activities for 12 years and older; MCID = minimum clinically important difference; MPPI = minimal patient perceivable improvement.

ACT

The Asthma Control Test (ACT) is a patient-reported tool used to assess asthma control among adolescents and adults; that is, patients who are 12 years of age and older. A working group consisting of primary care clinicians and asthma specialists from the US was formed to develop a list of 22 items that reflected the multidimensional nature of asthma control.[42] The 22-item survey was completed by recruited patients with asthma, and stepwise logistic regression analyses were used to identify the items with the greatest validity in discriminating between patients who differed in their specialists' ratings of asthma control.[42] Based on these analyses, investigators selected the following five items for inclusion in the ACT: shortness of breath, patient's rating of asthma control, use of rescue medication, role limitations due to asthma; and nocturnal asthma symptoms.[42] Each item is scored on a five-point scale, which ranges from one to five, with greater scores indicating better asthma control. Scores from the individual items are summed to produce an overall score ranging from five to 25.[42] Patients recall their relevant experiences during the previous four weeks.

The ACT was originally validated in a cross-sectional study of patients (N= 471) with asthma who were under the routine care of an asthma specialist.[42] In this study, researchers noted low and moderate correlation between the ACT and FEV_1 (r = 0.19; *P* = 0.0001) and specialists' ratings of asthma control (r = 0.45; *P* = 0.0001), respectively. The internal consistency reliability of the ACT was 0.84, which exceeds the 0.70 threshold thus indicating it is acceptable for use in clinical trials.[43] The researchers noted that ACT scores discriminated between groups of patients who differed in their specialists' ratings of asthma control, the need for change in their therapy (i.e., step down, no change, step up in therapy), and their % predicted FEV_1 values. A cut point of 19/25 demonstrated the highest area under the receiver operating characteristic (ROC) curve (0.727), and the overall agreement between the ACT and the specialist's rating was 74.1% at this cut point. Researchers have also validated the ACT in patients not previously followed by asthma specialists,[41] as well as a version administered over the Internet,[44] the telephone,[45] and in the home setting.[46] A systematic review of 21 studies (enrolling 11,141 patients) concluded that the ACT had good diagnostic accuracy for assessment of controlled and not well-controlled asthma: pooled sensitivity and specificity values at levels of controlled and not well-controlled asthma were 0.77 (95% CI, 0.68 to 0.84) and 0.84 (95% CI, 0.74 to 0.91), 0.75 (95% CI, 0.63 to 0.83) and 0.82 (95% CI, 0.76 to 0.87), respectively.[47] The study investigators, however, concluded poor accuracy of the ACT for the assessment of uncontrolled asthma: pooled sensitivity and specificity values of 0.49 (95% CI, 0.42 to 0.56) and 0.92 (95% CI, 0.86 to 0.96), respectively; and, a hierarchical summary ROC area under the curve of 0.69.[47]

Anchor-based methods were used to determine an MCID for the ACT in a study involving four independent samples of adults (n = 4,018) with asthma .[41] The anchor measures that were used varied between samples, but overall included: patient's self-report of asthma severity, patient's self-report of number of asthma episodes, spirometry values, specialist global assessment, specialist recommended change in therapy, patient self-report of change in asthma, short-acting beta-2 agonist dispensing greater than six canisters, and asthma exacerbations.[41] The difference in the mean ACT scores corresponding to the various anchor measures were calculated and used to determine the MCID, which ranged from 1.06 to 5.28, with an overall mean of 3.09 (95% CI, 2.68 to 3.50).[41] Many of the anchors used to determine this MCID do not consider the patient perspective, which is a

limitation of this method; however, the values reported for the self-reported change in asthma anchor, a patient-reported measure, are in support of the MCID (mean difference of 2.59 ranging from 1.06 to 3.83).

A distribution-based approach was also used to determine the MCID for the ACT, using the following criteria: 0.5 SD, 1 SEM, and 2 SEM.[41] A weighted mean based on the four sample populations was calculated: 2.21 for 0.5 SD, 1.96 for 1 SEM, and 3.91 for 2 SEM. Using this data, the study proposed a difference of three points as clinically meaningful across several of the measures described, which is in support of the MCID of 3.09 determined using anchor-based methods.[41]

AQLQ(S)12+

The Asthma Quality of Life Questionnaire with Standardized Activities for 12 years and older {AQLQ[S]12+) is a patient-reported, disease-specific, health-related quality of life measure that is a variant of the validated standardized version of the Asthma Quality of Life Questionnaire (AQLQ[S]) developed by Juniper et al.[48] To accommodate the larger group of patients with asthma in whom the instrument is intended to be used, that is patients who are12 years and older versus adults only, the developers of AQLQ(S) altered one question about “work-related limitations” to “work-/school-related limitations." [49] As with the original questionnaire, the AQLQ(S)12+ includes 32 questions grouped into four domains: symptoms, activity limitations, emotional function, and environmental stimuli. Each question is scored on a seven-point scale ranging from seven (no impairment) to one (severe impairment). The overall score is derived from the mean of the 32 questions, and therefore also ranges from one to seven with higher scores indicating less severe impairment. Further, the questionnaire may be reported by domain, which would include the mean of the scores for the questions corresponding to the domain of interest.[13] Patients score each item based on a recall of their experiences during the previous two weeks.

A post-hoc analysis of data collected from two phase III studies including asthma patients aged 12 and older was used to assess the validity of the AQLQ(S)12+.[50] Overall, the AQLQ(S)12+ showed high internal consistency at baseline based on a Cronbach’s alpha of 0.96 and 0.97 for the overall score of each of the two studies.[50,51] The internal consistency reliability for the subscales also ranged from 0.84 to 0.94.[52] Evidence of construct validity of the AQLQ(S)12+ was generated in a secondary analysis of two clinical trials, which included 2433 patients with asthma (baseline mean FEV_1 % predicted [range], ≥ 18 years: 75.4 [32 to 136] and 73.3 [41 to 107]; 12 to 17 years: 83.9 [47 to 125] and 77.8 [54 to114] in trials 1 and 2, respectively). [49] The cross-sectional (baseline) and longitudinal (baseline to end of study) construct validity between AQLQ(S)12+ and other measures of asthma clinical status — including FEV_1 percentage of predicted value, PEF, symptoms, night walking, and amount of rescue medication — was variable, with Pearson correlation coefficients indicating none to moderate associations. In a subsequent pooled analysis conducted by another group of researchers, however, the AQLQ(S)12+ demonstrated excellent overall test-retest reliability (intra-class correlation coefficients [ICC] of 0.86 in one study and 0.83 in the other), moderate to strong construct validity with other indices of asthma (i.e., the baseline Asthma Control Questionnaire score, and mean daytime and nighttime symptom diary scale scores), strong known-groups validity, and excellent responsiveness. [51] No study appears to have formally estimated the MCID for AQLQ(S)12+, although given the significant overlap between the AQLQ(S)12+ and the original Asthma Quality of Life Questionnaire, researchers consider a cut point of 0.5 to indicate a clinically important difference given this is the MCID for AQLQ(S).[49,51,53]

Total Daily Asthma Symptom Score

The total daily asthma symptom score is a patient-reported outcome that addresses the occurrence of asthma symptoms and their effect on daily activities and sleep. The score is divided into two parts: daytime and nighttime, both rated on ordinal scales. The daytime score consists of five items, from zero to five, and are recorded each evening. The nighttime score consists of four items, from zero to four, and is recorded each morning. A summary of the scoring for both parts is outlined in Table 43. Symptom scores were always completed prior to treatment visits and assessed before any spirometry or PEF measurements were taken. For the studies included in this report, a total daily asthma symptom score was defined as the average of the daytime and nighttime scores. A missing daytime or nighttime score was considered a missing total daily score.

No evidence regarding the validity or reliability of the total daily asthma symptom score was identified; however the assessment of symptoms is considered an acceptable clinical variable for the clinical investigation of the treatment of asthma, according to the European Medicines Agency (EMA).[19] The EMA guidance document recommends that daytime and nighttime symptoms are recorded using a diary to record symptoms,[19] which was done by the studies in this report.

Table 43: Daily Asthma Symptom Score, Daytime and Nighttime Scoring Scale

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

Appendix 6: Summary of Respiclick Device

To date, the most effective treatment available for asthma is the regular use of inhaled medications, which delivers the medication directly to the lungs and allows for optimal efficacy and safety.[10,14,54] The efficacy of this treatment is dependent on the correct use of the inhalers, which is a common issue for patients. There are many products and devices available on the market, providing options for patients to find an inhaler tailored to their needs, but the inhalation technique varies between products and this increases the chance of administration related error and consequently reduces the ability to control the disease.[55,56] This issue is reflected in multiple studies that have assessed patient preferences for attributes of inhalers, which frequently cited ease of use, functionality, and instructions that are simple and easy to follow as aspects of an inhaler that are important to patients. [10,14,52,57]

The product under review is fluticasone propionate multidose dry powder inhaler (Fp MDPI), indicated for the maintenance treatment of steroid-responsive bronchial asthma as prophylactic therapy in patients 12 years and older. The device used to administer this treatment is an inhalation-driven, multidose dry powder inhaler with active ingredients dispersed in a lactose monohydrate excipient and contained within a reservoir. [6-8] This product does not use propellants and has an integrated dose counter that measures the number of actuations used by the inhaler, which allows patients to monitor the use of their inhaler and when it needs to be replaced.[4] The manufacturer of Fp MDPI and FS MDPI provided several citations related to ease of use, device preference, and device satisfaction for the RespiClick inhaler. However, most of the references were for unpublished conference abstracts, which did not provide sufficient information to appraise. One published study (N = 120) provided by the manufacturer was a single site, single visit, randomized, crossover study assessing device technique mastery, handling errors, and preference using empty RespiClick [European name Spiromax] , Easyhaler, and Turbuhaler devices in healthy adult Finnish volunteers.[58] All three inhaler devices are designed to deliver dry powder drugs. Participants (aged 18 years or older), with no experience with dry powder inhaler devices in the 18 months before randomization, were observed by health care professionals to evaluate the proportion of participants achieving device mastery (defined as an absence of health care professional observed errors). Patients were randomly assigned to one of six inhaler device sequence groups. Each device was tested in three steps: intuitive use (with no instructions), after reading the patient information leaflet, and after health care professional instruction. Health care professionals monitored and recorded errors based on device-specific handling error checklists, developed according to the patient information leaflet per device. Participants completed a device preference questionnaire and rated their satisfaction with the three devices. Participants were primarily (66%) aged 20 to 29 years, almost all (99%) were educated to university level, and 75% were female. The study reported that RespiClick was correctly used by 37.5% and 93.3% of participants in steps 1 and 2, respectively, compared with 0% and 58.3% with Easyhaler, and 9.2% and 76.7% with Turbuhaler. All three devices were associated with high device mastery (> 95%) in step 3. The most common error reported with RespiClick was related to the orientation of the device, whereas not shaking the device was the most common error with Easyhaler. Errors in priming the device were the most common with Turbuhaler. Respiclick, Easyhaler, and Turbuhaler were rated as the “easiest device to use” by 73.1%, 12.6%, and 14.3% of participants, respectively. The authors concluded higher levels of device mastery and ease of use with RespiClick compared with Easyhaler and Turbuhaler. However, there are key limitations that limit the generalizability of the results, many of which

were noted by the authors of the article. First, receiving health care professional instructions clearly affects the use of all three devices; therefore, it is unclear whether there is a true advantage with RespiClick in the setting where no physician and/or pharmacist instruction on use is provided. (It is acknowledged that in clinical practice, adequate instruction is not always accessible or provided.) All participants were healthy adult volunteers and almost all had university-level education. It would been more informative to assess the inhaler devices in asthmatic patients without inhaler experience who are younger (at least 12 years of age, more in line with the indication), and with low education and literacy levels. Easyhaler is not available in Canada and therefore this comparison is less applicable to the clinical context in Canada. Although the results suggest greater ease of use with RespiClick with the assumption that this would translate into improved adherence and potential clinical outcomes, there is no data in this regard. Lastly, comparison with other dry powder inhalers that deliver Fp would potentially have been more informative.[58]

A second study provided by the manufacturer was a phase IIIb, 12-week, multicenter, double-blind, double-dummy, randomized controlled trial in patients (≥ 12 years) with persistent asthma designed primarily to demonstrate noninferiority of twice-daily budesonide/formoterol 160 mcg/4.5 mcg (delivered via the RespiClick [European name Spiromax] inhaler) to budesonide/formoterol 200 mcg/6 mcg (delivered via the Turbuhaler device) in change from baseline in weekly average of daily trough morning peak expiratory flow (N = 605).[59] Patient satisfaction and preference with the inhaler devices were assessed as the key secondary outcome. The study indicated that the mean difference in the total performance domains scores and scores for “device preference” and “willingness to continue” on the Satisfaction and Preference Questionnaire for RespiClick versus Turbuhaler were statistical significantly in favour of RespiClick. There were no statistically significant differences in the total convenience domain score between the two devices. Given that the study’s primary conclusion was noninferiority between the inhalers and that although there were statistical differences between groups for certain domains on the Satisfaction and Preference Questionnaire, the clinical significance of these findings is uncertain. It is unclear whether these would translate into improved adherence with treatment and longer-term outcomes. Of note, this study and the aforementioned one were funded by the manufacturer of Fp MDPI and FS MDPI.[59]

A supplemental literature search for studies that assessed patient preferences for asthma inhalers was performed in an effort to evaluate how Fp MDPI performs in comparison to other available products in terms of patient preference; however, studies pertaining specifically to this topic were not identified. A brief discussion of patient preferences on a broader scale has been summarized below to provide additional context for this review.

Of the many types of inhalers, pressurized metered-dose inhalers (pMDIs) and dry powder inhalers (DPIs) are the most commonly used for the treatment of asthma.[10,60] An observational comparative study in adults patients conducted in Lebanon evaluated the use of DPIs versus MDIs. In this sample, a higher percentage of DPI users performed the administration techniques correctly and reported finding the device easier to use, compared with MDI users. Also, a lower percentage of DPI users showed exacerbation of symptoms during therapy, in comparison to MDI users.[60] The difficulty associated with the use of a pMDI can in part, be attributed to a degree of coordination that is required to actuate an inhaler and inhalation.[61] Difficulty with coordination is a particular concern for older adults and children. [61] The use of a breath-actuated DPI eliminates this issue; however, patients have expressed concern about inhaling a dose during an attack with the use of a DPI.[14,52] A spacer may also be applied to aid the use of a pMDI by decreasing the coordination

required for use, although this also reduces the portability of the device because of the size and bulkiness.[56] Traditional pMDIs and DPIs are typically small and compact, which is another important attribute to patients that has also been suggested as a factor in adherence due to the portability of the device.[14,56]

Hygiene has also been indicated as a desirable attribute for inhalers by patients.[14,52,62] In one study aimed at determining patient preferences of adults with asthma, and the attitudes toward their inhalers through a semi-structured interview process, hygiene was identified as an area of interest under the “inhaler preference” theme of the interview.[14] The study reported concern among patients regarding the hygiene of pMDIs, as they had an issue with an easily removable lid and the buildup of dust, which can aggravate asthma.[14] Further, DPIs were considered more hygienic than pMDIs by this group.[14]

Lastly, patients frequently report that having a dose counter associated with their inhaler as a very important attribute, as it helps patients keep track of their medication and ensure they have enough remaining in the event of an attack.[10,14,56,62] Most DPIs have a dose counter, unlike pMDIs, which typically lack this feature.[56]

Appendix 7: Summary of Indirect Comparisons

Introduction

Aermony RespiClick (Fp MDPI) has been approved for treatment in adults and adolescents with asthma. Given that many other ICS products are already on the market and there is an absence of head-to-head studies that have compared Fp MDPI against these, the objective of this Appendix was to critically appraise the manufacturer submitted indirect comparison (IDC) that assesses the comparative efficacy and safety of FP MDPI versus other similar treatments.

Methods

The manufacturer submitted an IDC which was reviewed, summarized, and critically appraised.

Objectives and Rationale for Manufacturer's IDC

The primary objective of the manufacturer's IDC was to evaluate the efficacy and safety of FP MDPI (fluticasone propionate [FP; ICS]) and fluticasone propionate in combination with salmeterol xinafoate (FS; ICS-LABA) versus other available similar products for the treatment of asthma.

Study Eligibility and Selection Process

Literature Search

[redacted]

Table 44: Population, Interventions, Comparisons, Outcomes, and Study Design Criteria for Study Inclusion

Criteria	Description	
Population	[redacted]	
	[redacted]	
Interventions[†]	[redacted]	[redacted]

Criteria	Description
	[redacted]
Comparators	[redacted]
Outcomes	[redacted]
Study design	[redacted]
Language	[redacted]
Search period	[redacted]

HFA = hydrofluoroalkane; ICS = inhaled corticosteroid; LABA = long-acting beta-agonist.

[redacted]

Source: Manufacturer's network meta-analysis.[9]

Eligibility Criteria

[redacted]

Study Selection

[redacted]

Data Extraction

[redacted]

Table 45: Baseline Patient Demographic and Clinical Characteristics of Included Randomized Controlled Trials in the Evidence Base

Study Author/Year	Treatment	Male, n (%)	Age, Years Mean (SD)	Body Weight, kg Mean (SD)	BMI Mean (SD)	Race/Ethnicity				
						Caucasian, n (%)	Black, n (%)	Asian, n (%)	Hispanic, n (%)	Other, n (%)
ICS to Placebo										
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Study Author/Year	Treatment	Male, n (%)	Age, Years Mean (SD)	Body Weight, kg Mean (SD)	BMI Mean (SD)	Race/Ethnicity				
						Caucasian, n (%)	Black, n (%)	Asian, n (%)	Hispanic, n (%)	Other, n (%)
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Study Author/Year	Treatment	Male, n (%)	Age, Years Mean (SD)	Body Weight, kg Mean (SD)	BMI Mean (SD)	Race/Ethnicity				
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Study Author/Year	Treatment	Male, n (%)	Age, Years Mean (SD)	Body Weight, kg Mean (SD)	BMI Mean (SD)	Race/Ethnicity				
						Caucasian, n (%)	Black, n (%)	Asian, n (%)	Hispanic, n (%)	Other, n (%)
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Study Author/Year	Treatment	Male, n (%)	Age, Years Mean (SD)	Body Weight, kg Mean (SD)	BMI Mean (SD)	Race/Ethnicity				
						Caucasian, n (%)	Black, n (%)	Asian, n (%)	Hispanic, n (%)	Other, n (%)
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Study Author/Year	Treatment	Male, n (%)	Age, Years Mean (SD)	Body Weight, kg Mean (SD)	BMI Mean (SD)	Race/Ethnicity				
						Caucasian, n (%)	Black, n (%)	Asian, n (%)	Hispanic, n (%)	Other, n (%)
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Study Author/Year	Treatment	Male, n (%)	Age, Years Mean (SD)	Body Weight, kg Mean (SD)	BMI Mean (SD)	Race/Ethnicity				
						Caucasian, n (%)	Black, n (%)	Asian, n (%)	Hispanic, n (%)	Other, n (%)
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Study Author/Year	Treatment	Male, n (%)	Age, Years Mean (SD)	Body Weight, kg Mean (SD)	BMI Mean (SD)	Race/Ethnicity				
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Study Author/Year	Treatment	Male, n (%)	Age, Years Mean (SD)	Body Weight, kg Mean (SD)	BMI Mean (SD)	Race/Ethnicity				
						Caucasian, n (%)	Black, n (%)	Asian, n (%)	Hispanic, n (%)	Other, n (%)
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Study Author/Year	Treatment	Male, n (%)	Age, Years Mean (SD)	Body Weight, kg Mean (SD)	BMI Mean (SD)	Race/Ethnicity				
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Study Author/Year	Treatment	Male, n (%)	Age, Years Mean (SD)	Body Weight, kg Mean (SD)	BMI Mean (SD)	Race/Ethnicity				
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Study Author/Year	Treatment	Male, n (%)	Age, Years Mean (SD)	Body Weight, kg Mean (SD)	BMI Mean (SD)	Race/Ethnicity				
						Caucasian, n (%)	Black, n (%)	Asian, n (%)	Hispanic, n (%)	Other, n (%)
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Study Author/Year	Treatment	Male, n (%)	Age, Years Mean (SD)	Body Weight, kg Mean (SD)	BMI Mean (SD)	Race/Ethnicity				
						Caucasian, n (%)	Black, n (%)	Asian, n (%)	Hispanic, n (%)	Other, n (%)
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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Study Author/Year	Treatment	Male, n (%)	Age, Years Mean (SD)	Body Weight, kg Mean (SD)	BMI Mean (SD)	Race/Ethnicity				
						Caucasian, n (%)	Black, n (%)	Asian, n (%)	Hispanic, n (%)	Other, n (%)
	[redacted]									
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Study Author/Year	Treatment	Male, n (%)	Age, Years Mean (SD)	Body Weight, kg Mean (SD)	BMI Mean (SD)	Race/Ethnicity				
						Caucasian, n (%)	Black, n (%)	Asian, n (%)	Hispanic, n (%)	Other, n (%)
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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study Author/Year	Treatment	Male, n (%)	Age, Years Mean (SD)	Body Weight, kg Mean (SD)	BMI Mean (SD)	Race/Ethnicity				
						Caucasian, n (%)	Black, n (%)	Asian, n (%)	Hispanic, n (%)	Other, n (%)
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICS/LABA to Placebo										
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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ICS/LABA to ICS/LABA										
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Study Author/Year	Treatment	Male, n (%)	Age, Years Mean (SD)	Body Weight, kg Mean (SD)	BMI Mean (SD)	Race/Ethnicity				
						Caucasian, n (%)	Black, n (%)	Asian, n (%)	Hispanic, n (%)	Other, n (%)
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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Study Author/Year	Treatment	Male, n (%)	Age, Years Mean (SD)	Body Weight, kg Mean (SD)	BMI Mean (SD)	Race/Ethnicity				
						Caucasian, n (%)	Black, n (%)	Asian, n (%)	Hispanic, n (%)	Other, n (%)
Mixed										
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Study Author/Year	Treatment	Male, n (%)	Age, Years Mean (SD)	Body Weight, kg Mean (SD)	BMI Mean (SD)	Race/Ethnicity				
						Caucasian, n (%)	Black, n (%)	Asian, n (%)	Hispanic, n (%)	Other, n (%)
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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study Author/Year	Treatment	Male, n (%)	Age, Years Mean (SD)	Body Weight, kg Mean (SD)	BMI Mean (SD)	Race/Ethnicity				
						Caucasian, n (%)	Black, n (%)	Asian, n (%)	Hispanic, n (%)	Other, n (%)

BDP = beclomethasone diproprionate; BF = budesonide formeterol fumarate; BMI = body mass index; BUD = budesonide; CIC = ciclesonide; FF = fluticasone furorate; FV = fluticasone furorate and vilanterol; FP = fluticasone propionate; FS = fluticasone propionate and salmeterol xinafoate; ICS = inhaled corticosteroid; LABA = long-acting beta-agonist; MF = mometasone furoate; MFF = mometasone furoate and formoterol; SABA = short-acting beta-2 agonists; SD = standard deviation.

* Spread reported as range in text.
† Spread reported as SE in text.
‡ Converted to kg from lbs.

Source: Manufacturer's network meta-analysis.[9]

Comparators

[redacted]

Table 46: Categorization of ICS and ICS/LABA Treatments for High, Medium, and Low Dose

ICS or ICS/LABA Drug-Device	Total Daily Dose (Individual Dosage)		
	Low Dose	Medium Dose	High Dose
BF Symbicort Turbuhaler	[redacted]	[redacted]	[redacted]
BDP QVAR	[redacted]	[redacted]	[redacted]
BUD Pulmicort Turbuhaler	[redacted]	[redacted]	[redacted]
CIC Alvesco	[redacted]	[redacted]	[redacted]
FF Arnuity Ellipta	[redacted]	[redacted]	[redacted]
FV Breo Ellipta	[redacted]	[redacted]	[redacted]
FP Flovent	[redacted]	[redacted]	[redacted]
FP Flovent Diskus	[redacted]	[redacted]	[redacted]
FP Flovent HFA	[redacted]	[redacted]	[redacted]
FP MDPI	[redacted]	[redacted]	[redacted]
FS Advair Diskus	[redacted]	[redacted]	[redacted]
FS MDPI	[redacted]	[redacted]	[redacted]
FS Advair HFA	[redacted]	[redacted]	[redacted]
MF Asmanex Twisthaler	[redacted]	[redacted]	[redacted]

ICS or ICS/LABA Drug-Device	Total Daily Dose (Individual Dosage)		
	Low Dose	Medium Dose	High Dose
		[redacted]	
MFF Zenhale	[redacted]	[redacted]	[redacted]

BF = budesonide formoterol fumarate; BDP = beclomethasone dipropionate; BUD = budesonide; CIC = ciclesonide; FF = fluticasone furoate; FV = fluticasone furoate and vilanterol; FP = fluticasone propionate; FS = fluticasone propionate and salmeterol xinafoate; HFA= hydrofluoroalkane; ICS= inhaled corticosteroid; LABA= long-acting beta-2 agonist; MDPI= multidose dry powder inhaler; MF = mometasone furoate; MFF = mometasone furoate and formoterol.

Source: Manufacturer's network meta-analysis.[9]

Outcomes

[redacted]

Quality Assessment of Included Studies

[redacted]

Evidence Network

Figure 6: Network of Trials for Network Meta-Analysis for Non-SABA Treatments by Class

Figure 6 contained confidential information and was removed at the request of the manufacturer.

[redacted]

Indirect Comparison Methods

[redacted]

Results

[redacted]

[redacted]

[redacted]

Low-Dose Evidence Results

[redacted]

Table 47: Summary of NMA Results for the Outcomes in Low-Dose ICS and ICS/LABA Networks

Outcome	Low-Dose ICS
[redacted]	[redacted]

Outcome	Low-Dose ICS
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

ACT = Asthma Control Test; AE = adverse event, AQLQ(S): Asthma Quality of Life Questionnaire With Standardized Activities; BF = budesonide formoterol fumarate; BDP = beclomethasone dipropionate; BUD = budesonide; CIC = ciclesonide; FEV_1 = forced expiratory volume in 1 second; FF = fluticasone furoate; FV = fluticasone furoate and vilanterol; FP = fluticasone propionate; FS = fluticasone propionate and salmeterol xinafoate; MF = mometasone furoate; MFF = mometasone furoate and formoterol; NMA = network meta-analysis; PEF = peak expiratory flow.

Source: Manufacturer's network meta-analysis.[9]

Medium-Dose Evidence Results

[redacted]

Table 48: Summary of NMA Results for the Outcomes in Medium-Dose ICS and ICS/LABA Networks

Outcome	Medium-Dose ICS
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Outcome	Medium-Dose ICS
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

ACT = Asthma Control Test; AE = adverse event; AQLQ(S) = Asthma Quality of Life Questionnaire With Standardized Activities; BF = budesonide formoterol fumarate; BDP = beclomethasone dipropionate; BUD = budesonide; CIC = ciclesonide; FEV_1 = forced expiratory volume in 1 second; FF = fluticasone furoate; FV = fluticasone furoate and vilanterol; FP = fluticasone propionate; FS = fluticasone propionate and salmeterol xinafoate; MF = mometasone furoate; MFF = mometasone furoate and formoterol; PEF = peak expiratory flow.

Source: Manufacturer's network meta-analysis.[9]

High-Dose Evidence Results

[redacted]

Table 49: Summary of NMA Results for the Outcomes in High-Dose ICS and ICS/LABA Networks

Outcome	High-Dose ICS
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Outcome	High-Dose ICS
[redacted]	[redacted]
[redacted]	[redacted]

ACT = Asthma Control Test; AE = adverse event, AQLQ(S): Asthma Quality of Life Questionnaire With Standardized Activities; BF = budesonide formoterol fumarate; BDP = beclomethasone dipropionate; BUD = budesonide; CIC = ciclesonide; FEV_1 = forced expiratory volume in 1 second; FF = fluticasone furoate; FV = fluticasone furoate and vilanterol; FP = fluticasone propionate; FS = fluticasone propionate and salmeterol xinafoate; MF = mometasone furoate; MFF = mometasone furoate and formoterol; PEF = peak expiratory flow.
Source: Manufacturer's network meta-analysis.[9]

Critical Appraisal

[redacted]

[redacted]

[redacted]

[redacted]

Conclusion

[redacted]

Appendix 8: Summary of Phase I and II Trials

Introduction

To summarize the findings of one phase I and two phase II trials that assess the comparative pharmacokinetic and efficacy data of fluticasone propionate multidose dry powder inhaler (Fp MDPI) against products containing fluticasone propionate which are already available.

Findings

Objectives and Rationale

The primary objective of the phase I trial was to determine the pharmacokinetics and tolerability of high-dose Fp MDPI (and fluticasone propionate/ salmeterol xinofoate multidose dry powder inhaler [FS MDPI]) compared with high-dose Flovent Diskus (and Advair Diskus) in patients with asthma.[4,16,17,29]

The primary objectives of the phase II trials were to evaluate the dose response and to demonstrate superiority in efficacy of four doses of Fp MDPI compared with placebo. These studies also included an additional active-control Flovent Diskus arm to allow for numerical comparisons.[4,16,17,29]

Study Design

Study 10042 was a phase I, multicenter, open-label, randomized, active-controlled, four-period crossover, single-dose study (N = 40).

The two phase II trials, Study 201 (N = 622) and Study 202 (N = 640), were randomized, double-blind placebo- and open-label active-controlled, parallel-group, multicenter, 12-week dose-ranging trials in patients 12 years and older with asthma. Patients had to have a best forced expiratory volume in one second (FEV_1) of 40% to 85% of predicted values for age, height, sex, and race, and demonstrated post-bronchodilator reversibility (at least 15% in Study 201 and at least 12% in Study 202). Study 201 was conducted in patients with asthma who were uncontrolled on nonsteroidal maintenance therapy, whereas Study 202 was conducted in patients with asthma who remained symptomatic despite high-dose inhaled corticosteroids (ICS) therapy.

Both phase II trials were designed with a two-week run-in period during which patients continued using their current asthma medications and were also instructed to administer one inhalation of placebo MDPI (single-blind) twice daily. At the end of the run-in period, patients who met the eligibility criteria were randomized to one of six treatment groups at a 1:1:1:1:1:1 ratio using a stratified permuted block.

Intervention and Comparators

The evaluated treatments for each of these studies are summarized in Table 50. Study 202 was the only study that included all three doses of Fp MDPI currently marketed (50 mcg, 100 mcg, and 200 mcg). These doses are now referred to as 55 mcg, 113 mcg, and 232 mcg, respectively, in order to represent their metered dose per inhalation.

Table 50: Evaluated Treatments in Phase I and Phase II Studies

Study 10042	Study 201	Study 202
Fp MDPI 232 mcg x 1 inhalation	Placebo MDPI x 1 inhalation b.i.d.	Placebo MDPI x 1 inhalation b.i.d.
FS MDPI 232 mcg/14 mcg x 1 inhalation	Fp MDPI 12.5 mcg x 1 inhalation b.i.d.	Fp MDPI 50 mcg x 1 inhalation b.i.d.
Flovent Diskus 250 mcg x 2 inhalations	Fp MDPI 25 mcg x 1 inhalation b.i.d.	Fp MDPI 100 mcg x 1 inhalation b.i.d.
Advair Diskus 500 mcg/50 mcg x 1 inhalation	Fp MDPI 50 mcg x 1 inhalation b.i.d.	Fp MDPI 200 mcg x 1 inhalation b.i.d.
	Fp MDPI 100 mcg x 1 inhalation b.i.d.	Fp MDPI 400 mcg x 1 inhalation b.i.d.
	Flovent Diskus 100 mcg x 1 inhalation b.i.d.	Flovent Diskus 250 mcg x 1 inhalation b.i.d.

b.i.d. = twice daily; Fp MDPI = fluticasone propionate multidose dry powder inhaler; FS MDPI = fluticasone propionate/ salmeterol xinofoate multidose dry powder inhaler.

Source: Health Canada Reviewer's Report[2]; FDA Medical Report.[4]

Outcomes

In Study 10047, the systemic levels of fluticasone propionate were compared between formulations for pharmacokinetic outcomes, such as the area under the curve from time zero up to the last measurable concentration (AUC_{0-t}), the maximum measured concentration of the analyte in plasma (C_{max}), and the area under the curve from time zero extrapolated to infinite time ($AUC_{0-\infty}$).

In studies 201 and 202, the primary end point was a change from baseline in trough FEV_1 over the 12-week treatment period, which was to be carried out in the full analysis set.

Statistical Analysis

No statistical analysis plan was reported in the documents submitted to the CADTH Common Drug Review for Study 10042.

In studies 201 and 202, the primary end point was the change from baseline trough FEV_1 over the 12-week treatment period. The primary analysis was performed using a mixed model repeated measure (MMRM) analysis with effects due to baseline trough FEV_1, sex, age, visit, treatment, and visit-by-treatment interaction. For the four dose levels, a fixed-sequence multiple testing procedure was used to control for overall type I error at the 0.05 level. Initially, there was to be a test for the two-sided linear in log-dose time-averaged trend, which was first performed at a 0.05 level of significance. If this trend test demonstrated overall efficacy of Fp MDPI to be significantly positive, the highest Fp MDPI dose tested was to be compared with placebo with a two-sided test at the 0.05 level of significance. If this Fp MDPI dose resulted in a statistically significantly greater mean change in FEV_1 than placebo, the next highest Fp MDPI dose was compared with placebo with a two-sided test at the 0.05 level of significance. This testing was to proceed through the lower doses until an Fp MDPI dose was not found to be statistically significantly different from placebo, or if all other doses had been tested. The primary analyses were conducted on the full analyses set population, with a last observation carried forward approach used to handle missing data. Sensitivity analyses were conducted based on analysis of covariance (ANCOVA). Comparisons of the Fp MDPI dose groups and Flovent Diskus were also examined based on an MMRM analysis, similar to the primary analyses comparing Fp MDPI doses with placebo. There were no adjustments for multiplicity in these comparisons.

Study Populations

Study 10047

Study 10047 was conducted in patients aged 12 years and older with persistent asthma. Forty patients were recruited to participate in this study, with an average age of 29.6 years (range: 12 and 72 years). Fifty-six per cent of the patients were male, and 72% of the patients were white.

Study 201

In Study 201, 909 patients with asthma received run-in placebo MDPI. A total of 622 patients were randomized in this study and comprised the intention-to-treat population (ITT) (Table 53), of which 139 (22%) prematurely discontinued treatment. This study used predetermined stopping criteria for worsening asthma, based on post-baseline lung function tests, such as FEV_1 falling below 80% of baseline value, or incidence of asthma exacerbation. This criteria resulted in the withdrawal of 19% of patients in the placebo groups, compared with 4% to 8% in the active groups. A total of 38 patients were discontinued due to a protocol violation, which consisted of less than 80% adherence to the study drug or any protocol deviation deemed by the clinical study leader as a protocol violation, and resulted in 6% total patient withdrawals. The placebo (10%) and Fp MDPI 12.5 mcg twice daily (9%) groups had the highest rates of dropout due to protocol violation.

Demographics and baseline disease characteristics were similar across treatment groups. There was a slightly higher total percentage of females (58%) than males (42%), and higher proportion of whites (85%) overall. All patients were to demonstrate at least 15% reversibility of disease, and the mean reversibility was 26.9% at screening overall. The overall mean percentage predicted FEV_1 was 66% at screening, with a mean overall baseline FEV_1 of 2.2 L.

Table 51: Patient Demographics and Disposition in Study 201

	Number (%) of Patients					
	Fp MDPI				Placebo b.i.d.	Flovent Diskus 100 mcg b.i.d.
	12.5 mcg b.i.d.	25 mcg b.i.d.	50 mcg b.i.d.	100 mcg b.i.d.		
Patient Disposition, N (%)						
Number of patients randomized	103	104	104	103	104	104
Number of patients withdrawn from study	24 (23)	21 (20)	12 (12)	21 (20)	41 (39)	20 (19)
Met stopping criteria for worsening of asthma	8 (8)	7 (7)	4 (4)	9 (9)	20 (19)	6 (6)
Protocol violation	9 (9)	6 (6)	5 (5)	2 (2)	10 (10)	6 (6)
Patient withdrawal	4 (4)	2 (2)	2 (2)	5 (5)	5 (5)	1 (<1)
Adverse event	0	0	0	1 (<1)	2 (2)	2 (2)
Full analysis set	102 (99)	101 (97)	102 (98)	102 (99)	102 (98)	102 (98)
Patient Demographics						
Age, years, mean (SD)	41.0 (16.94)	42.4 (16.02)	39.1 (16.06)	36.9 (15.34)	39.7 (15.28)	40.0 (15.34)
Men, N (%)	46 (45)	41 (39)	44 (42)	43 (42)	49 (47)	43 (42)
White, N (%)	91 (88)	91 (88)	90 (87)	85 (83)	85 (82)	85 (82)

	Number (%) of Patients					
	Fp MDPI				Placebo b.i.d.	Flovent Diskus 100 mcg b.i.d.
	12.5 mcg b.i.d.	25 mcg b.i.d.	50 mcg b.i.d.	100 mcg b.i.d.		
Black, N (%)	10 (10)	11 (11)	12 (12)	14 (14)	17 (16)	17 (16)
Asian, N (%)	1 (< 1)	2 (2)	2 (2)	4 (4)	0	1 (< 1)
BMI, kg/m^2 mean (SD)	29 (7)	28 (6)	28 (7)	30 (8)	28 (7)	28 (7)
Baseline Characteristics (ITT Analysis Set)						
Baseline FEV_1, L, mean (SD)	2.3 (0.69)	2.2 (0.59)	2.2 (0.63)	2.3 (0.66)	2.3 (0.62)	2.2 (0.66)
Baseline FEV_1 % predicted, mean (SD)	66.6 (11.80)	67.5 (10.50)	66.3 (11.15)	66.4 (11.61)	66.4 (11.14)	65.3 (11.74)
Baseline airway reversibility %, mean (SD)	26.7 (12.01)	26.0 (11.86)	24.3 (10.63)	27.6 (12.92)	30.6 (17.84)	26.2 (12.50)

b.i.d. = twice daily; FEV_1 = forced expiratory volume in one second; Fp MDPI = fluticasone propionate multidose dry powder inhaler; ITT = intention to treat; SD = standard deviation.

Source: Health Canada Reviewer's Report[2]; FDA Medical Report.[4]

Study 202

In Study 202, patients with severe persistent asthma whose previous asthma was uncontrolled on a high dose of ICS (1000 mcg per day of Flovent Diskus or an equivalent ICS]) were enrolled. Current asthma therapy could include stable high-dose ICS monotherapy or ICS/long-acting beta-2 agonist combination for at least four weeks. A list of permitted therapies and daily dosage ranges is provided in Table 52.

Table 52: Permitted ICS or ICS/LABA Medications for Study 202 or Equivalent

Asthma Therapy	Daily Dose (mcg/day)
Fluticasone propionate HFA MDI	≥ 880 mcg
Fluticasone propionate DPI	≥ 1,000 mcg
Beclomethasone dipropionate DPI or HFA (Clenil Modulite)	≥ 2,000 mcg
Beclomethasone dipropionate HFA (QVAR)	≥ 640 mcg
Budesonide DPI or MDI	≥ 1,600 mcg
Flunisolide	≥ 2,000 mcg
Triamcinolone acetonide	≥ 2,000 mcg
Mometasone furoate DPI	≥ 880 mcg
Ciclesonide HFA MDI	≥ 640 mcg

DPI = dry powder inhaler; HFA = hydrofluoroalkane; ICS = inhaled corticosteroids; LABA = long-acting beta-2 agonist; MDI = metered-dose inhaler.

Source: Health Canada Reviewer's Report.[2]

A total of 1,238 patients were screened for enrolment into this study, and 889 patients were considered to be eligible for enrolment during the run-in period. A total of 640 patients were randomized to treatment and were in the ITT population (Table 53). Patients appeared to be balanced between treatment groups with respect to age, race, and weight. The mean baseline FEV_1 score ranged from 1.96 to 2.11 L (Table 54), and the mean baseline percentage of predicted FEV_1 ranged from 62.5% to 65.3% across groups. Mean reversibility was generally similar across groups (27% to 32%). Of the patients randomized, 181 (28%) withdrew prematurely. The most common reason for withdrawal was that patients had met stopping criteria for worsening of asthma, for which there were 31% in the placebo group, and 12% to 18% in the active groups.

Table 53: Patient Demographics and Disposition in Study 202

	Number (%) of patients					
	Fp MDPI				Placebo b.i.d.	Flovent Diskus 250 mcg b.i.d.
	50 mcg b.i.d.	100 mcg b.i.d.	200 mcg b.i.d.	400 mcg b.i.d.		
Patient Disposition, N (%)						
Number of patients randomized	107	107	106	107	106	107
Number of patients withdrawn from study	25 (23)	20 (19)	31 (29)	27 (25)	48 (45)	30 (28)
Met stopping criteria for worsening of asthma	16 (15)	13 (12)	19 (18)	16 (15)	33 (31)	15 (14)
Protocol violation	5 (5)	4 (4)	10 (9)	6 (6)	8 (8)	12 (11)
Patient withdrawal	1 (<1)	1 (< 1)	0	2 (2)	4 (4)	2 (2)
Adverse event	1 (<1)	1 (< 1)	1 (< 1)	1 (< 1)	1 (< 1)	0
Full analysis set	107 (100)	106 (> 99)	102 (96)	107 (100)	105 (> 99)	103 (96)
Patient Demographics						
Age, years, mean (SD)	47.9 (14.59)	48.7 (12.48)	47.7 (14.18)	50.9 (13.32)	49.8 (12.87)	49.2 (13.26)
Men, N (%)	44 (41)	52 (49)	40 (38)	35 (33)	41 (39)	49 (46)
White, N (%)	96 (90)	94 (88)	93 (88)	91 (85)	96 (91)	95 (89)
Black, N (%)	9 (8)	12 (11)	12 (11)	13 (12)	8 (8)	11 (10)
Asian, N (%)	1 (< 1)	1 (< 1)	1 (< 1)	2 (2)	2 (2)	0 (0)
BMI, kg/m^2 mean (SD)	31 (18)	30 (8)	30 (8)	30 (7)	31 (9)	30 (6)
Baseline Characteristics (ITT Analysis Set)						
Baseline FEV_1, L, mean (SD)	2.11 (0.66)	2.031 (0.551)	1.999 (0.525)	2.016 (0.636)	1.984 (0.565)	1.955 (0.529)
Baseline FEV_1 % predicted, mean (SD)	63.7 (10.9)	63.1 (9.5)	63.4 (12.1)	65.3 (11.4)	63.1 (10.0)	62.5 (12.1)
Baseline airway reversibility %, mean (SD)	31.6 (22.4)	27.3 (14.7)	30.4 (25.2)	29.1 (19.5)	28.9 (19.1)	26.8 (15.7)

b.i.d.= twice daily; FEV_1= forced expiratory volume in one second; Fp MDPI = fluticasone propionate multidose dry powder inhaler; ITT = intention to treat; SD= standard deviation.

Source: Health Canada Reviewer's Report[2]; FDA Medical Report.[4]

Results

Efficacy

Study 201

The mean change from baseline in trough FEV_1 values ranged from 0.136 L to 0.271 L across treatment groups. Statistically significant differences were observed when comparing Fp MDPI 25 mcg, 50 mcg, and 100 mcg twice daily with placebo; however, no statistically significant differences were observed between the Fp MDPI 12.5 mcg twice daily treatment group and placebo (Table 54). When compared with Flovent Diskus 100 mcg twice daily, there were no statistically significant differences observed between any of the Fp MDPI doses and the active control as all comparisons had confidence intervals crossing zero. Flovent Diskus 100 mcg twice daily was statistically significantly superior to placebo.

Table 54: Change in FEV_1 (L) from Baseline to Week 12 by Treatment Group by Full Analysis Set Using Mixed Model for Repeated Measures in Study 201

	Number (%) of Patients					
	Fp MDPI				Placebo b.i.d. (N = 102)	Flovent Diskus 100 mcg b.i.d. (N = 102)
	12.5 mcg b.i.d. (N = 102)	25 mcg b.i.d. (N = 101)	50 mcg b.i.d. (N = 102)	100 mcg b.i.d. (N = 102)		
Baseline FEV_1, mean	2.237 (0.6880)	2.228 (0.6098)	2.225 (0.6391)	2.264 (0.6645)	2.227 (0.5957)	2.191 (0.6708)
FEV_1 (L) at week 12, mean (SE)	2.412 (0.7016)	2.531 (0.7207)	2.480 (0.6663)	2.553 (0.7109)	2.490 (0.7275)	2.472 (0.5891)
LS mean difference in FEV_1 (L) from baseline to week 12, mean (SE) (95% CI)	0.189 (0.0389) (0.112 to 0.266)	0.268 (0.0380) (0.194 to 0.343)	0.263 (0.0367) (0.190 to 0.335)	0.295 (0.0388) (0.219 to 0.371)	0.145 (0.0412) (0.064 to 0.226)	0.234 (0.0367) (0.162 to 0.306)
LS mean difference (L) from placebo b.i.d. (95% CI)	0.044 (–0.068 to 0.155)	0.123 (0.013 to 0.233)	0.117 (0.009 to 0.226)	0.150 (0.039 to 0.261)	–	0.113 (0.034, 0.192)
P value	0.4395	0.0286	0.0339	0.0084	–	0.005
LS mean difference (L) from Flovent Diskus 100 mcg b.i.d. (95% CI)	–0.042 (–0.146 to 0.061)	0.039 (–0.063 to 0.141)	0.030 (–0.070 to 0.130)	0.062 (–0.041 to 0.165)	–0.083 (–0.190 to 0.023)	–
P value	0.4204	0.4515	0.5542	0.2382	0.1255	–

b.i.d.= twice daily; CI = confidence interval; FEV_1= forced expiratory volume in one second; Fp MDPI = fluticasone propionate multidose dry powder inhaler; ITT = intention to treat; SE= standard error.

Source: Health Canada Reviewer's Report[2]; FDA Medical Report.[4]

Study 202

In all treatment groups, there was an increase in least squares mean FEV_1 from baseline over the 12-week treatment period, with the smallest change seen in the placebo group. The primary analysis, which was the trend test of linear log-dose response in change from baseline in trough FEV_1 over 12 weeks, did not show a statistically significant differences between Fp MDPI doses. Therefore, based on the hierarchical analysis plan, planned comparisons between the doses of Fp MDPI and placebo could not be interpreted with respect to statistical significance. Regardless, in pairwise comparisons there was no evidence of treatment effects for any of the Fp MDPI doses compared with placebo. Comparisons between Flovent Diskus 250 mcg twice daily and placebo were also not different, which raises questions about assay sensitivity of the study.[29] The results for the primary end point based on MMRM is provided in Table 55. There were no significant differences observed in any of the four Fp MDPI doses compared with Flovent Diskus 250 mcg.

Table 55: Change in FEV_1 (L) from Baseline to Week 12 by Treatment Group by Full Analysis Set Using Mixed Model for Repeated Measures in Study 202

	Number (%) of Patients					
	Fp MDPI				Placebo b.i.d. (N = 105)	Flovent Diskus 250 mcg b.i.d. (N = 103)
	50 mcg b.i.d. (N = 107)	100 mcg b.i.d. (N = 106)	200 mcg b.i.d. (N = 102)	400 mcg b.i.d. (N = 107)		
Baseline FEV_1 mean (SD)	2.078 (0.6336)	2.069 (0.5806)	2.008 (0.5695)	2.015 (0.6294)	2.005 (0.5478)	1.987 (0.5426)
FEV_1 at week 12 mean (SD)	2.140 (0.6214)	2.190 (0.6660)	2.204 (0.5959)	2.108 (0.6140)	2.094 (0.6640)	2.215 (0.6724)
LS mean difference in FEV_1 from baseline to week 12, mean (SE) (95% CI)	0.060 (0.0327) (–0.004 to 0.125)	0100 (0.0322) (0.037 to 0.163)	0.148 (0.0338) (0.081 to 0.214)	0.101 (0.0332) (0.035 to 0.166)	0.049 (0.0366) (–0.023 to 0.121)	0.145 (0.0334) (0.079 to 0.210)
LS mean difference from placebo (95% CI)	0.011 (–0.085 to 0.107)	0.051 (–0.045 to 0.147)	0.099 (0.001 to 0.196)	0.052 (–0.045 to 0.148)	–	–
P value	0.8155	0.2950	0.0473	0.2922	–	–
LS mean difference from Flovent DIskus 250 mcg	–0.080 (–0.172 to 0.012)	–0.043 (–0.135 to 0.049)	0.009 (–0.085 to 0.102)	–0.040 (–0.133 to 0.053)	–0.090 (–0.187 to 0.008)	–
P value	0.0869	0.3565	0.8526	0.3999	0.0716	–

b.i.d.= twice daily; CI = confidence interval; FEV_1= forced expiratory volume in one second; Fp MDPI = fluticasone propionate multidose dry powder inhaler; ITT = intention to treat; SE= standard error.

Source: FDA Medical and Statistical Reports.[4,29]

Pharmacokinetic Data

Phase I Study

In Study 10042, following a single-dose administration of Fp MDPI (200 mcg x 1 inhalation) compared with FS MDPI (200 mcg/ 12.5 mcg x one inhalation), Advair Diskus (500 mcg/ 50 mcg x 1 inhalation), and Flovent Diskus (250 mcg x 2 inhalations), the systemic exposure (combination of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) to fluticasone propionate was 20% to 30% lower with Fp MDPI than with Flovent Diskus; however, the systemic exposure was similar between FS MDPI and Advair Diskus.

Table 56: Fluticasone Propionate Pharmacokinetics Descriptive Statistics in Phase I Study

Parameter	Treatment	N	Geometric LS Mean	GMR	90% CI
AUC_{0-t} (pg▪h/mL) Mean (SD)	Fp MDPI Flovent Diskus	36 36	593.25 744.04	0.797	0.72 to 0.88
	Fp MDPI FS MDPI	36 36	593.20 544.77	1.089	0.98 to 1.21
	FS MDPI Advair Diskus	36 36	545.48 566.96	0.962	0.87 to 1.07
C_{max} (pg/mL) Mean (SD)	Fp MDPI Flovent Diskus	37 37	66.41 78.28	0.848	0.77 to 0.93
	Fp MDPI FS MDPI	37 37	66.48 61.24	1.085	0.99 to 1.19
	FS MDPI Advair Diskus	36 36	61.92 61.62	1.005	0.92 to 1.10
$AUC_{0-\infty}$ (pg▪h/mL) Mean (SD)	Fp MDPI Flovent Diskus	30 30	616.45 812.91	0.758	0.69 to 0.83
	Fp MDPI FS MDPI	25 25	623.60 583.68	1.068	0.96 to 1.19
	FS MDPI Advair Diskus	28 28	586.85 618.51	0.949	0.86 to 1.04

$AUC_{0-\infty}$ = area under the curve from time zero extrapolated to infinite time; $AUC_{0-\infty}$ = area under the curve from time zero up to the last measurable concentration; CI = confidence interval; C_{max} = maximum measured concentration of analyte in plasma; Fp MDPI = fluticasone propionate multidose dry powder inhaler; FS MDPI = fluticasone propionate/salmeterol xinafoate multidose dry powder inhaler; GMR = geometric mean ratio; LS = least squares; pg/mL = picogram per millilitre; pg▪h/mL = picogram hour per millilitre; SD = standard deviation.

Source: FDA Medical and Statistical Reports.[4,29]

Phase II Studies

The pharmacokinetic analysis set of patients in the phase II trials included a total of 185 patients, and results are displayed in Table 57. In the pharmacokinetic analysis, the C_{max} and AUC_{0-t} of fluticasone propionate increased with increasing doses of Fp MDPI and comparisons indicated approximate dose proportional increases across the Fp MDPI doses tested. On a mcg per mcg basis, the systemic exposures from Fp MDPI were consistently higher than that of Flovent Diskus, according to Health Canada.

Table 57: Fluticasone Propionate Pharmacokinetics Descriptive Statistics in Phase II Studies

Study 201					
	Fp MDPI				Flovent Diskus 100 mcg b.i.d. (N = 21)
	12.5 mcg b.i.d. (N = 16)	25 mcg b.i.d. (N = 22)	50 mcg b.i.d. (N = 19)	100 mcg b.i.d. (N = 17)	
AUC_{0-t} (pg•h/mL) Mean (SD)	21.6 (27.09)	42.0 (23.21)	63.2 (22.64)	153.8 (91.42)	103.4 (45.65)
C_{max} (pg/mL) Mean (SD)	5.4 (4.23)	10.0 (5.35)	12.9 (5.13)	33.6 (15.49)	23.4 (10.73)
T_{max} (h) Median	1.1 (0.2 to 4.0)	1.0 (0.1 to 12.0)	1.0 (0.3 to 12.0)	0.8 (0.2 to 4.0)	1.0 (0.3 to 12.0)
Study 202					
	Fp MDPI				Flovent Diskus 250 mcg b.i.d. (N = 16)
	50 mcg b.i.d. (N = 18)	100 mcg b.i.d. (N = 18)	200 mcg b.i.d. (N = 18)	400 mcg b.i.d. (N = 20)	
AUC_{0-t} (pg•h/mL) Mean (SD)	117.6 (145.79)	126.8 (33.73)	292.0 (162.28)	462.8 (262.45)	162.3 (74.79)
C_{max} (pg/mL) Mean (SD)	19.1 (15.53)	26.5 (6.18)	55.2 (29.12)	83.0 (44.32)	32.5 (13.92)
T_{max} (h) Median	1.0 (0.2 to 2.0)	0.9 (0.2 to 8.0)	1.1 (0.3 to 12.0)	0.8 (0.1 to 12.0)	1.1 (0.5 to 12.0)

$AUC_{0-\infty}$ = area under the curve from time zero extrapolated to infinite time; AUC_{0-t} = area under the curve from time zero up to the last measurable concentration; b.i.d. = twice daily; C_{max} = maximum measured concentration of analyte in plasma; Fp MDPI = fluticasone propionate multidose dry powder inhaler; h = hours; LS = least squares; pg/mL = picogram per millilitre; pg•h/mL = picogram hour per millilitre; SD = standard deviation.

Source: Health Canada Reviewer's Report.[2]

Critical Appraisal

There was a higher rate of premature discontinuation in the placebo group of studies 201 (39%) and 202 (45%) compared with those in active treatment groups (18% in Study 201 and 25% in Study 202). Missing data for these trials were imputed using the last observation carried forward approach. As a result, there is potential for filled-in data to be distorted, and for precision in these data points to be overstated. The main reason for discontinuation in the placebo group was due to stopping criteria for worsening asthma, which included a decrease in FEV_1 below 80% of their baseline value. The stopping criteria put in place for these phase II studies may have decreased the treatment effect in these studies. Also, the nature of the discontinuations signals that these were not at random; a key assumption for the MMRM analysis is missing-at-random missingness. FDA tipping point analyses, however, confirmed the conclusions from the primary analysis for Study 201, but because the null hypothesis for the primary analysis could not be rejected in Study 202, the FDA did not conduct sensitivity analyses (Center for Drug Evaluation and Research US Food and Drug Administration, 2017 #3). Finally, the high rate of withdrawal due to lack of efficacy in the placebo group may suggest that blinding may have been compromised in these groups.

Baseline asthma severity was evaluated by FEV_1, and the mean pre-bronchodilator per cent predicted FEV_1 for the phase II trials ranged from 62% to 68%. These values indicate that patients in these trials were suboptimally treated for their asthma prior to enrolment in the studies. Therefore, results might be biased in favour of the active treatment groups

because patients in these groups would have their treatment dose improved while placebo patients would have their suboptimal active ICS switched to placebo. Finally, the majority of patients enrolled in the phase II studies were white (87%), which may limit the generalizability of these results to other races.

Conclusions

Fp MDPI was compared with Flovent Diskus, a product currently marketed in Canada with identical medicinal ingredients, in one phase I and two phase II trials. Study 10042 suggested that after administration of a high-strength dose of Fp MDPI, FS MDPI, Advair Diskus, and Flovent Diskus, the systemic exposure of fluticasone propionate is approximately 20% to 30% lower with the Fp MDPI inhaler versus Flovent Diskus, and similar between FS MDPI and Advair Diskus. Studies 201 and 202 suggested that there were no statistically significant differences observed between the Fp MDPI doses currently marketed and Flovent Diskus 100 mcg and 250 mcg for change in trough FEV_1 over 12 weeks, but this does not necessarily indicate equivalence or noninferiority between these two products. [redacted]

References

1. Health fact sheets: chronic conditions, 2016. Ottawa: Statistics Canada; 2017.
2. *Health Canada reviewer's report: Aermony RespiClick (fluticasone propionate) [**CONFIDENTIAL** internal report].* Ottawa: Therapeutics Products Directorate, Health Canada; 2017.
3. *Aermony RespiClick (fluticasone propionate): 55 mcg, 113 mcg, 232 mcg inhalation powder [product monograph].* Toronto (ON): Teva Canada Limited; 2017.
4. Center for Drug Evaluation and Research U.S. Food and Drug Administration. Medical review(s). *ArmonAir RespiClick (fluticasone propionate). Company: Teva Pharmaceutical Industries Ltd. Application no.: 208798. Approval date: 01/27/2017*. Rockville (MD): FDA; 2017.
5. Responses to questions for Health Canada regarding Aermony and Arbesda MDPIs [**CONFIDENTIAL** additional Health Canada's information]. Ottawa (ON): Health Canada; 2018.
6. *Clinical Study Report: FSS-AS-301. A 12-week, double-blind, placebo-controlled, efficacy and safety study of fluticasone propionate multidose dry powder inhaler compared with fluticasone/salmeterol multidose dry powder inhaler in adolescent and adult patients with persistent asthma symptomatic despite low-dose or mid-dose inhaled corticosteroid therapy [**CONFIDENTIAL** internal manufacturer's report].* Frazer (PA): Teva Branded Pharmaceutical Products R&D; 2016.
7. *Clinical Study Report: FSS-AS-30017. A 12-week, double-blind, placebo-controlled, efficacy and safety study of fluticasone propionate multidose dry powder inhaler compared with fluticasone/salmeterol multidose dry powder inhaler in adolescent and adult patients with persistent asthma symptomatic despite inhaled corticosteroid therapy [**CONFIDENTIAL** internal manufacturer's report].* Frazer (PA): Teva Branded Pharmaceutical Products R&D; 2016.
8. *Clinical Study Report: FSS-AS-305. A 26-week open-label study to assess the long-term safety of fluticasone propionate multidose dry powder inhaler and fluticasone propionate/salmeterol multidose dry powder inhaler in patients 12 years of age and older with persistent asthma [**CONFIDENTIAL** internal manufacturer's report].* Frazer (PA): Teva Branded Pharmaceutical Products R&D; 2016.
9. Systematic literature review and network meta-analysis of RespiClick™ in combination with inhaled corticosteroid (ICS) in asthma treatments. Technical report. *CDR submission: Aermony RespiClick (fluticasone propionate), 55 mcg, 113 mcg, 232 mcg, an inhaled corticosteroid (ICS). Company: Treva Canada Innovation [**CONFIDENTIAL** manufacturer's submission]*. Montreal (QC): Teva Canada Innovation; 2017.
10. Ding B, Small M, Scheffel G, Holmgren U. Maintenance inhaler preference, attribute importance, and satisfaction in prescribing physicians and patients with asthma, COPD, or asthma-COPD overlap syndrome consulting for routine care. *Int J Chron Obstruct Pulmon Dis.* 2018;13:927-936.
11. Emeryk A, Pirozynski M, Emeryk-Maksymiuk J. Dry powder inhalers - between the doctor and the patient. *Adv Respir Med.* 2018;86(1):44-52.
12. van der Palen J, Thomas M, Chrystyn H, et al. A randomised open-label cross-over study of inhaler errors, preference and time to achieve correct inhaler use in patients with COPD or asthma: comparison of Ellipta with other inhaler devices. *NPJ Prim Care Respir Med.* 2016;26:16079.
13. Usmani OS, Lavorini F, Marshall J, et al. Critical inhaler errors in asthma and COPD: a systematic review of impact on health outcomes. *Respiratory Research.* 2018;19(1):10.
14. Jahedi L, Downie SR, Saini B, Chan HK, Bosnic-Anticevich S. Inhaler technique in asthma: how does it relate to patients' preferences and attitudes toward their inhalers? *Journal of Aerosol Medicine and Pulmonary Drug Delivery.* 2017;30(1):42-52.
15. Kopel LS, Phipatanakul W, Gaffin JM. Social disadvantage and asthma control in children. *Paediatr Respir Rev.* 2014;15(3):256-262.
16. 2.7.4 Summary of clinical safety. Fluticasone propionate multidose dry powder inhaler (Fp MDPI). *CDR submission: Aermony RespiClick (fluticasone propionate), 55 mcg, 113 mcg, 232 mcg, an inhaled corticosteroid (ICS). Company: Treva Canada Innovation [**CONFIDENTIAL** manufacturer's submission]. Montreal (QC): Teva Canada Innovation; 2017 Oct 4.* Montreal (QC): Teva Canada Innovation; 2017.
17. 2.7.3 Summary of clinical efficacy. Fluticasone propionate multidose dry powder inhaler (Fp MDPI). *CDR submission: Aermony RespiClick (fluticasone propionate), 55 mcg, 113 mcg, 232 mcg, an inhaled corticosteroid (ICS). Company: Treva Canada Innovation [**CONFIDENTIAL** manufacturer's submission]. Montreal (QC): Teva Canada Innovation; 2017 Oct 4.* Montreal (QC): Teva Canada Innovation; 2017.
18. *Flovent® HFA (fluticasone propionate inhalation aerosol): 50, 125, and 250 mcg/metered dose; FLOVENT® DISKUS® (fluticasone propionate powder for inhalation): 100, 250, AND 500 mcg/blister [product monograph].* Mississauga (ON): GlaxoSmithKline Inc.; 2016.
19. *Arnuity™ Ellipta® (fluticasone furoate dry powder for oral inhalation): 100 mcg and 200 mcg [product monograph].* Mississauga (ON): GlaxoSmithKline Inc.; 2017.
20. *Asmanex® Twisthaler® (mometasone furoate dry powder inhaler): 100 mcg, 200 mcg, 400 mcg /metered inhalation [product monograph].* Kirkland (QC): Merck Canada Inc.; 2018.
21. *Alvesco® (ciclesonide inhalation aerosol): 100 mcg and 200 mcg/ actuation (ex-valve) [product monograph].* Mississauga (ON): AstraZeneca Canada Inc.; 2017.
22. *Pulmicort® Turbuhaler® (budesonide): 100 mcg, 200 mcg, and 400 mcg / metered dose [product monograph].* Mississauga (ON): AstraZeneca Canada Inc.; 2017.
23. *Qvar™ (beclomethasone dipropionate) metered dose aerosol 50 ìg and 100 mg [product monograph].* Laval (QC): Valeant Canada LP; 2013.

24. National Heart Lung and Blood Institute. *Guidelines for the diagnosis and management of asthma. Summary report 2007.* Bethesda (MD): The Institute; 2007.

25. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J.* 2005;26(2):319-338.

26. Raphael G, Yiu G, Sakov A, Liu S, Caracta C. Randomized, double-blind trial evaluating the efficacy and safety of fluticasone propionate and fluticasone propionate/salmeterol delivered via multidose dry powder inhalers in patients with persistent asthma aged 12 years and older. *Journal of Asthma.* 2018;55(6):640-650.

27. Sher LD, Yiu G, Sakov A, Liu S, Caracta CF. Fluticasone propionate and fluticasone propionate/salmeterol multidose dry powder inhalers compared with placebo for persistent asthma. *Allergy Asthma Proc.* 2017;38(5):343-353.

28. *CDR submission: Aermony RespiClick (fluticasone propionate), 55 mcg, 113 mcg, 232 mcg, an inhaled corticosteroid (ICS). Company: Treva Canada Innovation [**CONFIDENTIAL** manufacturer's submission].* Montreal (QC): Teva Canada Innovation; 2017.

29. Center for Drug Evaluation and Research U.S. Food and Drug Administration. Statistical review(s). *ArmonAir Respiclick (fluticasone propionate). Company: Teva Pharmaceutical Industries Ltd. Application no.: 208798. Approval date: 01/27/2017*. Rockville (MD): FDA; 2017.

30. Mansfield L, Yiu G, Sakov A, Liu S, Caracta C. A 6-month safety and efficacy study of fluticasone propionate and fluticasone propionate/salmeterol multidose dry powder inhalers in persistent asthma. *Allergy and Asthma Proceedings.* 2017;38(4):264-276.

31. 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;14(1):23-27.

32. *Teva Branded Pharmaceutical Products R&D response to April 10, 2018 CDR request for additional information regarding the Aermony RespiClick (fluticasone propionate) CDR review: clinical study reports with appendices [**CONFIDENTIAL** additional manufacturer's information].* Montreal (QC): Teva Branded Pharmaceutical Products R&D; 2018.

33. Center for Drug Evaluation and Research U.S. Food and Drug Administration. *Non-inferiority clinical trials to establish effectiveness: guidance for industry.* Silver Spring (MD): FDA; 2016.

34. Reddel HK, Taylor DR, Bateman ED, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med.* 2009;180(1):59-99.

35. Fuhlbrigge A, Peden D, Apter AJ, et al. Asthma outcomes: exacerbations. *J Allergy Clin Immunol.* 2012;129(3 Suppl):S34-S48.

36. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med.* 2000;343(5):332-336.

37. FitzGerald JM, Boulet LP, McIvor RA, Zimmerman S, Chapman KR. Asthma control in Canada remains suboptimal: the Reality of Asthma Control (TRAC) study. *Can Respir J.* 2006;13(5):253-259.

38. Enright PL, Beck KC, Sherrill DL. Repeatability of spirometry in 18,000 adult patients. *Am J Respir Crit Care Med.* 2004;169(2):235-238.

39. Paik J, Scott LJ, Pleasants RA. Fluticasone propionate/salmeterol MDPI (AirDuo RespiClick): a review in asthma. *Clin Drug Investig.* 2018.

40. Vutikullird AB, Gillespie M, Song S, Steinfeld J. Pharmacokinetics, safety, and tolerability of a new fluticasone propionate multidose dry powder inhaler compared with fluticasone propionate Diskus in healthy adults. *Journal of Aerosol Medicine and Pulmonary Drug Delivery.* 2016;29(2):207-214.

41. Schatz M, Kosinski M, Yarlas AS, Hanlon J, Watson ME, Jhingran P. The minimally important difference of the Asthma Control Test. *J Allergy Clin Immunol.* 2009;124(4):719-723.

42. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol.* 2004;113(1):59-65.

43. *Health-related quality of life outcomes: issues in critical appraisal and interpretation.* Ottawa (ON): CADTH; 2018.

44. Koolen BB, Pijnenburg MW, Brackel HJ, et al. Validation of a web-based version of the asthma control test and childhood asthma control test. *Pediatr Pulmonol.* 2011;46(10):941-948.

45. Schatz M, Zeiger RS, Drane A, et al. Reliability and predictive validity of the Asthma Control Test administered by telephone calls using speech recognition technology. *J Allergy Clin Immunol.* 2007;119(2):336-343.

46. Schatz M, Mosen DM, Kosinski M, et al. Validity of the Asthma Control Test completed at home. *Am J Manag Care.* 2007;13(12):661-667.

47. Jia CE, Zhang HP, Lv Y, et al. The Asthma Control Test and Asthma Control Questionnaire for assessing asthma control: systematic review and meta-analysis. *J Allergy Clin Immunol.* 2013;131(3):695-703.

48. Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the Asthma Quality of Life Questionnaire. *Chest.* 1999;115(5):1265-1270.

49. 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.* 2005;3:58.

50. Juniper EF, Bousquet J, Abetz L, Bateman ED, GOAL Committee. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. *Respir Med.* 2006;100(4):616-621.

51. 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;20(6):903-912.

52. Hawken N, Torvinen S, Neine ME, et al. Patient preferences for dry powder inhaler attributes in asthma and chronic obstructive pulmonary disease in France: a discrete choice experiment. *BMC Pulm Med.* 2017;17(1):99.

53. 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;105(5):698-712.

54. Zervas E, Samitas K, Gaga M. Assessment of satisfaction with different dry powder inhalation devices in Greek patients with COPD and asthma: the ANASA study. *Int J Chron Obstruct Pulmon Dis.* 2016;11:1845-1855.

55. Bjermer L. The importance of continuity in inhaler device choice for asthma and chronic obstructive pulmonary disease. *Respiration.* 2014;88(4):346-352.

56. Chrystyn H, Price D. Not all asthma inhalers are the same: factors to consider when prescribing an inhaler. *Prim Car Respir J.* 2009;18(4):243-249.

57. Price D, Harrow B, Small M, Pike J, Higgins V. Establishing the relationship of inhaler satisfaction, treatment adherence, and patient outcomes: a prospective, real-world, cross-sectional survey of US adult asthma patients and physicians. *World Allergy Organ J.* 2015;8(1):26, 2015.

58. Sandler N, Hollander J, Langstrom D, Santtila P, Saukkonen A, Torvinen S. Evaluation of inhaler handling-errors, inhaler perception and preference with Spiromax, Easyhaler and Turbuhaler devices among healthy Finnish volunteers: a single site, single visit crossover study (Finhaler). *BMJ Open Respir Res.* 2016;3(1):e000119.

59. Virchow JC, Rodriguez-Roisin R, Papi A, Shah TP, Gopalan G. A randomized, double-blinded, double-dummy efficacy and safety study of budesonide-formoterol Spiromax(R) compared to budesonide-formoterol Turbuhaler(R) in adults and adolescents with persistent asthma. *BMC Pulm Med.* 2016;16:42.

60. Ramadan WH, Sarkis AT. Patterns of use of dry powder inhalers versus pressurized metered-dose inhalers devices in adult patients with chronic obstructive pulmonary disease or asthma: An observational comparative study. *Chronic Respir Dis.* 2017;14(3):309-320.

61. Chrystyn H. The Diskus: a review of its position among dry powder inhaler devices. *International Journal of Clinical Practice.* 2007;61(6):1022-1036.

62. Gustafsson P, Taylor A, Zanen P, Chrystyn H. Can patients use all dry powder inhalers equally well? *International Journal of Clinical Practice, Supplement.* 2005(149):13-18.