CADTH

CADTH COMMON DRUG REVIEW

Common Drug Review New Combination Product

fluticasone propionate / salmeterol xinafoate (Arbesda RespiClick)

(Teva Canada Innovation)

Indication: For the treatment of asthma in patients aged 12 years and older

Service Line:	CADTH Common Drug Review
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Abbreviations

ACMA	Asthma Canada Member Alliance
AE	adverse event
AQLQ(S)	Asthma Quality of Life Questionnaire with Standardized Activities
AUC	area under the curve
b.i.d.	twice daily
BMI	body mass index
BCLA	British Columbia Lung Association
CI	confidence interval
DPI	dry powder inhaler
FEF	forced expiratory flow
FEV_1	forced expiratory volume in one second
FEV_1 $AUEC_{0\text{-}12\ h}$	forced expiratory volume in one second from zero to 12 hours post dose
Fp	fluticasone propionate
Fp MDPI	fluticasone propionate multidose dry powder inhaler
FS DPI	fluticasone propionate / salmeterol xinafoate dry powder inhaler
FS MDPI	fluticasone propionate / salmeterol xinafoate multidose dry powder inhaler
FVC	forced vital capacity
HFA	hydrofluoroalkane
ICS	inhaled corticosteroid
ITT	intention-to-treat
LABA	long-acting beta2 agonist
LS	least squares
MCID	minimal clinically important difference
MDPI	multidose dry powder inhaler
MMRM	mixed model for repeated measures
P	probability
PEF	peak expiratory flow
RCT	randomized controlled trial
SABA	short-acting beta2 agonist
SAE	serious adverse event
SD	standard deviation
SE	standard error
TLA–O	The Lung Association – Ontario

Drug	Fluticasone propionate / salmeterol xinafoate (Arbesda RespiClick; FS MDPI)
Indication	For the treatment of asthma in patients aged 12 years or older
Reimbursement Request	As per indication
Manufacturer	Teva Canada Innovation

Executive Summary

Introduction

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

Arbesda RespiClick (fluticasone propionate / salmeterol xinafoate) is a twice daily fixed-dose combination of an inhaled corticosteroid (ICS), fluticasone propionate, and a long-acting beta2 agonist (LABA), salmeterol xinafoate, (in full, ICS/LABA). It has been approved in Canada for the maintenance treatment of steroid-responsive bronchial asthma in patients 12 years of age or older. Arbesda RespiClick is administered via multidose dry powder inhaler (MDPI) for patients requiring ICS/LABA therapy. Fluticasone propionate is a corticosteroid with potent anti-inflammatory properties, specifically including inhibition of immune cells and mediator production or secretion, while salmeterol xinafoate stimulates beta2 receptors, resulting in long-acting bronchodilator effects on the bronchi. The combination of fluticasone propionate and salmeterol xinafoate has previously been approved for the treatment of asthma in other inhaled products in Canada, such as Advair hydrofluoroalkane (HFA) and Advair Diskus. The doses of Advair Diskus (100 mcg /50 mcg, 250 mcg/50 mcg, and 500 mcg/50 mcg) and Advair HFA (125 mcg, 250 mcg) are higher than those of Arbesda RespiClick (55 mcg/14 mcg, 113 mcg/14 mcg, 232 mcg/14 mcg of fluticasone propionate / salmeterol xinafoate). The RespiClick delivery device is a breath-actuated, metered MDPI with the active ingredients dispersed in lactose monohydrate and contained within a reservoir. A metered dose of drug is delivered to a dose cup via air pulse activation when the cap is opened. Upon inhalation, the fluticasone propionate / salmeterol xinafoate is delivered to the airways as a fine powder.[2]

Another drug product submitted to CADTH in conjunction with this version of fluticasone propionate / salmeterol xinafoate is Aermony RespiClick (Fp MDPI), in which fluticasone propionate is delivered via MDPI as monotherapy.

Results and Interpretation

Included Studies

The evidence put forward for this review was drawn from three multi-centre, phase III randomized controlled trials: Study 301 (N = 647),[3] Study 30017 (N = 728),[4] and Study 305 (N = 674).[5] Two of these trials — Study 301 and Study 30017 — were 12-week, placebo-controlled, double-blind, dose-ranging, parallel-group trials designed to evaluate efficacy.[3,4]

The third study, Study 305, was a 26-week, open-label, active-comparator trial designed to evaluate safety.[5]

The two 12-week, double-blind placebo-controlled efficacy trials, Study 301 and Study 30017, were conducted in patients ≥ 12 years of age with persistent asthma who were not optimally controlled on their current low-, medium-, or high-dose ICS therapy. In both of these studies, fluticasone propionate / salmeterol xinafoate multidose dry powder inhaler (FS MDPI) was compared with Fp MDPI or placebo.[3,4] The studies were identical in design; however, the studies tested different drug doses. In Study 301, patients were assigned to low-dose (55 mcg/14 mcg) FS MDPI or medium-dose (113 mcg/14 mcg) FS MDPI twice daily, low-dose (55 mcg) Fp MDPI or medium-dose (113 mcg) Fp MDPI twice daily, or placebo. In Study 30017, patients were assigned to medium-dose (113 mcg/14 mcg) FS MDPI or high-dose (232 mcg/14 mcg) FS MDPI twice daily, medium-dose (113 mcg) Fp MDPI or high-dose (232 mcg) Fp MDPI twice daily, or placebo. The primary efficacy end point for both trials was to demonstrate superiority of FS MDPI at doses of 55 mcg/14 mcg, 113 mcg/14 mcg, and 232 mcg/14 mcg compared with Fp MDPI doses or placebo for a change from baseline in trough forced expiratory volume in one second ($FEV_{1)}$ at week 12. Both studies also evaluated patient-reported outcomes as well as safety and tolerability in comparison with placebo. Salbutamol HFA (or albuterol HFA, depending on availability), a short-acting beta2 agonist 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 treatment of ICS or ICS/LABA therapy and switched to low-dose ICS monotherapy (beclomethasone dipropionate 40 mcg HFA metered-dose inhaler or Fp MDPI 55 mcg) until randomization to either FS MDPI or placebo.[3,4]

The 26-week open-label, active-controlled safety trial, Study 305, was conducted in patients 12 years or older with an FEV_1 ≥ 40% of that which was predicted based on age, height, sex and race, and an established treatment regimen of preventive asthma therapy for eight weeks or longer.[5] The objective of this study was to assess the safety of medium-strength (113 mcg/14 mcg) and high-strength (232 mcg/14 mcg) fluticasone propionate / salmeterol xinafoate delivered via MDPI compared with medium-strength (250 mcg/50 mcg) and high-strength (500 mcg/50 mcg) fluticasone propionate / salmeterol xinafoate delivered via dry powder inhaler (FS DPI). The primary end points in this study were the type and incidence of adverse events (AEs) 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 FS MDPI and FS DPI. Based on this assumption, the principal efficacy variable for this study was a change from baseline in trough FEV_1 over the 26-week treatment period, with a noninferiority margin pre-specified as −0.125 L.[5]

There were a number of limitations noted within the clinical trials. Firstly, the efficacy studies (Study 301 and Study 30017) are limited by their short duration of 12 weeks. The primary outcome in these studies was 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 comparisons of FS MDPI dosage strengths were made with placebo, rather than with an active drug. Furthermore, there was a higher proportion of withdrawals in the placebo arms than in the FS MDPI arms, which were generally due to worsening asthma. Sensitivity analyses were conducted on early withdrawals, 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 FS MDPI and pooled arms of active comparator, FS DPI. Comparisons between the individual dosing arms were also reported. These comparisons do not appear to be adjusted for multiplicity, which would limit their interpretation.

Efficacy

In the 12-week efficacy studies, Study 301 and Study 30017, all treatment arms of FS MDPI showed a statistically significant improvement in change from baseline trough FEV_1 at 12 weeks when compared with placebo. In Study 301, the difference from placebo in trough FEV_1 for those taking 55 mcg/14 mcg FS MDPI was 0.266 L (95% confidence interval [CI], 0.172, 0.360, $P < 0.0001$); for those taking 113 mcg/14 mcg FS MDPI, it was 0.262 L (95 C, 0.168, 0.356, $P <0.0001$). For the same outcome in Study 30017, the difference from placebo in those taking 113 mcg/14 mcg FS MDPI was 0.274 L (95% CI, 0.189, 0.360, $P <0.0001$); in those taking 232 mcg/14 mcg FS MDPI, it was 0.276 L (95% CI, 0.191, 0.361, $P <0.0001$). Little evidence is available on the minimal clinically important difference for FEV_1. Between-group differences in trough FEV_1 between FS MDPI and Fp MDPI were statistically significantly in favour of FS MDPI, with absolute differences ranging from 0.092 L to 0.152 L; however, the clinical significance of the differences is uncertain. Secondary outcomes, such as rescue short-acting beta2 agonist daily use, and the Asthma Quality of Life Questionnaire (Standardised) and asthma symptoms scores, were generally supportive of efficacy for the three doses compared with placebo.[3-5]

The 26-week Study 305 was first and foremost a safety study. However, it reported having a power of 90% for demonstrating noninferiority of the pooled arms of FS MDPI 131 mcg/14 mcg and 232 mcg/14 mcg compared with the pooled arms of FS DPI 250 mcg/50 mcg and 500 mcg/50 mcg, for change from baseline in trough FEV_1 over the 26-week treatment period, with a noninferiority margin pre-specified as −0.125 L. Results for this outcome were not included by the manufacturer in this report; however, the treatment effect and lower limit of the 95% CI exceeded the −0.125 L noninferiority margin when the pooled arms of FS MDPI and FS DPI were compared (least squares mean difference): 0.029 L (95% CI, 0.036, 0.085, $P = 0.3821$). The baseline values for trough FEV_1 in the FS MDPI and the FS DPI arms were similar between groups (range: 2.310 L to 2.550 L). The treatment differences at the different dose levels, which appeared to be a post hoc analysis, were 0.000 L (SE: 0.0485) between the FS MDPI 113 mcg/14 mcg and FS DPI 250 mcg/50 mcg arms (95% CI, −0.095, 0.095, $P = 0.9966$) and 0.059 L between FS MDPI 232 mcg/14 mcg and FS DPI 500 mcg/50 mcg arms (95% CI, −0.032, 0.150, $P = 0.2056$).

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

Harms

In Study 301 and Study 30017, the frequency of patients reporting any treatment-emergent AEs was similar between FS MDPI (range: 41% to 42%) and placebo (36%). The incidence of patients who had experienced a serious AE, severe AE, or an AE causing withdrawal was low (< 3%) in all arms. In Study 301, asthma exacerbation was reported to have occurred at least once in seven patients (5%) in the placebo arm compared with three patients (2%) in the FS MDPI 55 mcg/14 mcg arm, and one patient (< 1%) in the FS MDPI 113 arm/14 mcg arm. In Study 30017, asthma exacerbation was reported to have occurred at least once in 23 patients (16%) in the placebo arm, compared with three patients (2%) in the FS MDPI 113 mcg/14 mcg arm, and six patients (4%) in the FS MDPI 232 mcg/14 mcg arm. The most frequently reported AEs across treatment arms in both studies were headache (6% in Study 301, 4% in Study 30017), nasopharyngitis (6% in Study 301, 7% in Study 30017), upper respiratory tract infection (3% in Study 301, 4% in Study 30017), and oral candidiasis (2% in Study 301 and Study 30017). One death was reported due to fulminant liver failure in Study 30017; it occurred in the FS MDPI 113 mcg/14 mcg arm.

The results of the long-term (26-week) safety trial, Study 305, were consistent with the results of Study 301 and Study 30017. The incidence of patients reporting treatment-emergent AEs across treatment arms FS MDPI and FS DPI were similar (70% in FS MDPI arms and 69% in FS DPI arms). The most frequently occurring AEs reported across all treatment arms 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 effects observed in Study 301 and Study 30017. Oral candidiasis was reported for ≤ 5% of subjects in the FS MDPI arms, 11% of subjects in the FS DPI 500 mcg/50 mcg arm, and 5% of subjects in the FS DPI 250 mcg /50 mcg arm, appearing to be dependent on the dose of ICS.

Cost

At the submitted price for each dose strength (ranging from $61.04 to $103.73 per MDPI containing 60 actuations), the manufacturer reported that FS MDPI would represent cost savings ranging from $0.66 to $1.30 per day when compared with the total daily drug costs of the individual component medications. The manufacturer also reported that when compared with other ICS/LABA fixed-dose combinations, FS MDPI may be a slight cost saving, except when compared with budesonide/formoterol.

The CADTH Common Drug Review consulted a clinical expert during the course of the review. The clinical expert indicated that there is the potential for prescribers or patients to double the number of actuations of FS MDPI per day to match their usual Fp dose, which would negate cost savings and could lead to increased costs. The CADTH Common Drug Review noted that the uncertainty regarding the comparative effectiveness of FS MDPI compared with the individual components of the fixed-dose combination and with other ICS/LABA combinations, and the lack of information available to assess the comparative doses for the individual strengths of FS MDPI. As a result, it is difficult to draw any definitive conclusions on comparative costs, given the uncertainty associated with the comparative efficacy data and the paucity of data regarding the comparative doses for the individual strengths of FS MDPI.

Other Considerations

The clinical studies (Study 301, Study 30017, and Study 305) included in this review evaluated both Fp MDPI and FS MDPI. In this review, only the efficacy and safety of FS MDPI were evaluated. The efficacy and safety of Fp MDPI have been considered in a separate report.

Supportive data from a phase II dose-ranging study were summarized (Appendix 4). The results of the study indicated that FS MDPI is not statistically significantly different from Advair Diskus in standardized baseline-adjusted FEV_1 area under the curve (AUC) over 12 hours post-dose. The studies were not designed to allow conclusions related to equivalence or noninferiority.

Conclusions

Three parallel-group randomized controlled trials (RCTs) were discussed in this review, which recruited patients 12 years and older with asthma who were inadequately controlled on ICS. Patients were included in studies in which two different doses of Fp MDPI were compared against Fp MDPI, placebo, or FS DPI for a minimum of 12 weeks and up to 26 weeks. There is very little comparative evidence for the use of FS MDPI versus alternative ICS/LABA combination therapies. Consequently, no concrete conclusions can be drawn with respect to the comparative effects of FS MDPI on asthma exacerbations. Supportive data from one phase II dose-ranging study suggested no statistically significant difference between standardized baseline-adjusted FEV_1 AUC over 12 hours post-dose between medium-dose Advair Diskus and the currently marketed FS MDPI 113 mcg/14 mcg dose; though, this does not necessarily mean the FS products are equivalent or noninferior to each other. FS MDPI was found to be significantly superior to placebo with respect to lung function. Results from the phase III efficacy studies suggest that compared with placebo, FS MDPI 55/14 mcg, 113 mcg/14 mcg, and 232 mcg/14 mcg improved FEV_1, reduced the incidence of worsening asthma, and increased the number of days without asthma symptoms throughout 12 weeks. FS MDPI was also associated with statistically significant differences in asthma quality of life with standardized activities and use of rescue medication when compared against placebo; however, these results are limited by their short duration and incomplete data sets.

No rigorous assessment of patient preferences regarding the 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/LABA in patients with asthma, the submitted data do not provide evidence for the long-term effects of FS MDPI; longer-term comparative studies would be useful to elucidate the benefits and harms of FS MDPI beyond 26 weeks of exposure. At the submitted prices for each dose strength, FS MDPI would represent cost savings ranging from $0.66 to $1.30 per day when compared with the total daily drug costs of the individual component medications. FS MDPI would also represent cost savings when compared with most other ICS/LABA inhalers, though it is difficult to draw any definitive conclusions on the comparative costs, given the uncertainty associated with the comparative efficacy data and the paucity of data regarding the comparative doses for the individual strengths of FS MDPI with other ICS/LABA inhalers.

Table 1: Summary of Key Results from Efficacy Trials

End Points	Study 301			Study 30017		
	Placebo	FS MDPI 55 mcg/14 mcg b.i.d.	FS MDPI 113 mcg/ 14 mcg b.i.d.	Placebo	FS MDPI 113 mcg/ 14 mcg b.i.d.	FS MDPI 232 mcg/14 mcg b.i.d.
Change from Baseline in Trough FEV_1 Over 12 Weeks (L)						
N	129	128	126	143	140	145
Baseline (SE)	2.188 (0.5628)	2.302 (0.6526)	2.162 (0.5522)	2.141 (0.0571)	2.157 (0.0537)	2.083 (0.0542)
LS mean change from baseline (SE)	0.053 (0.0350)	0.319 (0.0350)	0.315 (0.0352)	−0.004 (0.0312)	0.271 (0.0311)	0.272 (0.0307)
LSMD (95% CI) versus PLC [b]	–	0.266 (0.172, 0.360)	0.262 (0.168, 0.356)	–	0.274 (0.189, 0.360)	0.276 (0.191, 0.361)
Standardized[a] Baseline-Adjusted FEV_1 $AUEC_{0\text{-}12\ h}$ (L) Over 12 Weeks						
N	60	56	61	61	58	68
Baseline (SE)	2.253 (0.0694)	2.197 (0.0821)	2.228 (0.0735)	2.088 (0.0797)	2.095 (0.0803)	2.108 (0.0808)
LS mean change from baseline (SE)	0.074 (0.0487)	0.399 (0.0479)	0.408 (0.0465)	0.121 (0.0472)	0.442 (0.0496)	0.446 (0.0463)
LSMD (95% CI) versus PLC [b]	–	0.325 (0.203, 0.447)	0.335 (0.216, 0.453)	–	0.322 (0.212, 0.432)	0.326 (0.221, 0.431)
Change in Weekly Average of Self-Rated Total Daily Asthma Symptoms Scores (0-9) From Baseline Over 12 Weeks						
N	128	128	125	142	141	145
Baseline (SE)	0.796 (0.0356)	0.778 (0.0424)	0.777 (0.0418)	0.881 (0.0470)	0.950 (0.0489)	0.936 (0.0458)
LS mean change from baseline (SE)	−0.135 (0.0318)	−0.329 (0.0314)	−0.364 (0.0318)	−0.087 (0.0342)	−0.364 (0.0332)	−0.391 (0.0328)
LSMD (95% CI) versus PLC [b]	–	−0.194 (−0.279, −0.109)	−0.230 (−0.315, −0.144)	–	−0.277 (−0.370, −0.184)	−0.304 (−0.397, −0.212)
Change From Baseline in Weekly Mean Number of Inhalations of Rescue Medication (Albuterol or Salbutamol) per 24 Hours Over 12 Weeks or End Point						
N	129	128	126	143	141	145
Baseline (SE)	1.4 (0.11)	1.2 (0.10)	1.1 (0.11)	1.7 (0.15)	2.0 (0.17)	1.9 (0.16)
LS mean change from baseline (SE)	−0.003 (0.0937)	−0.706 (0.0930)	−0.677 (0.0937)	0.168 (0.1102)	−0.821 (0.1080)	−0.898 (0.1069)
LSMD (95% CI) versus PLC [b]	–	−0.704 (−0.957, −0.450)	−0.675 (−0.928, −0.421)	–	−0.989 (−1.291, −0.686)	−1.066 (−1.365, −0.766)
Change From Baseline AQLQ(S) at Week 12 or End Point						
N	110	108	109	129	135	131
Baseline (SE)	4.921 (0.0958)	5.142 (0.0807)	4.991 (0.1023)	4.924 (0.0794)	4.899 (0.0857)	4.967 (0.0374)
LS Mean	0.207 (0.0770)	0.539 (0.0770)	0.815 (0.0764)	−0.089 (0.0747)	0.592 (0.0725)	0.534 (0.0741)
LSMD (95% CI) versus PLC [b]	–	0.332 (0.125, 0.540)	0.608 (0.402, 0.814)	–	0.681 (0.478, 0.885)	0.623 (0.418, 0.828)

ANCOVA = analysis of covariance; AQLQ(S) = Asthma Quality of Life Questionnaire with Standardized Activities; b.i.d. = twice daily; CI= confidence interval; FEV_1= forced expiratory volume in one second; FEV_1 $AUEC_{0\text{-}12\ h}$ = standardized baseline-adjusted area under the effect curve for forced expiratory volume in one second from zero to 12 hours post dose; FS MDPI = fluticasone propionate / salmeterol xinafoate multidose dry powder inhaler; HR = hazard ratio; KM = Kaplan–Meier; LS = least squares; LSMD = least squares mean difference; N = total number in the sample under study; PLC = placebo; SE = standard error.

[a] FEV_1 $AUEC_{0\text{-}12\ h}$ was standardized by dividing the baseline-adjusted FEV_1 $AUEC_{0\text{-}1\ h}$ at week 12 by the number of hours between the start time of the dosage administration and the end of time of the last non-missing FEV_1 measurement.

[b] Least squares mean adjusted in the ANCOVA model with adjustment for baseline FEV_1, sex, age, (pooled) centre, previous therapy (inhaled corticosteroid or inhaled corticosteroid and long-acting beta2 agonist), and treatment. Missing data are imputed using the modified baseline-observation carried forward.

Source: Clinical study reports.[3-5]

1. Product Information

1.1 Health Canada–Approved Indications

Indication(s) to be Reviewed by the CADTH Common Drug Review
For the treatment of asthma in patients aged 12 years or older

1.2 Requested Listing Criteria

The requested listing criteria are in line with the indication submitted to Health Canada for approval and for the indication to be reviewed by the CADTH Common Drug Review (CDR).

Requested Listing Criteria
For the treatment of asthma in patients aged 12 years or older

1.3 Manufacturer's Rationale and Place in Therapy for the Combination

1.3.1 Rationale

Fluticasone propionate / salmeterol xinafoate multidose dry powder inhaler (FS MDPI) is an inhaled corticosteroid (ICS) with a long-acting beta2 agonist (LABA) (in full, ICS/LABA) administered through a new multidose dry powder inhaler (MDPI) that represents a safe, efficacious, and intuitive option in the management of asthma. ICSs suppress the chronic inflammation of asthma and reduce airway hyper-responsiveness. LABAs act on different aspects of the pathophysiology of asthma. In addition to affecting bronchodilation, they also inhibit mast cell mediator release and plasma exudation, and may reduce sensory nerve activation.

These two drug classes address complementary aspects of the pathophysiology of asthma that neither drug can achieve alone. There are several positive interactions between ICS and LABA that may optimize each other's beneficial actions in the airways, with the low systemic effects of the drugs not resulting in any increase in AEs.[6] A landmark study in 1994 demonstrated that patients with asthma who were not controlled on a low dose of ICS had little improvement if the dose was increased, but had much greater improvement if salmeterol was added.[2] The superiority of adding salmeterol instead of increasing the dose of ICS was confirmed in more severe asthmatic patients[7] and subsequently in a meta-analysis of nine studies, all indicating that the addition of salmeterol was superior to doubling (or more) the dose of ICS.[8] This was further shown in the addition of formoterol to ICS, which was more effective than a four-fold increase in the dose of inhaled budesonide in patients with moderate and severe asthma — a benefit that persisted for the 12 months of the study, demonstrating that tolerance does not develop with prolonged treatment.[9]

The use of ICS and LABA in combination has been incorporated into treatment guidelines across the world, with the combination inhaler being preferred in most countries, including Canada. This is due to the fact that a combination inhaler offers theoretical advantages both for maintenance of control, and as part of guided asthma self-management strategies and action plans, which prompt patient-initiated adjustments to reliever and controller therapy.[10-12] The Canadian Thoracic Society Asthma Committee has further published a commentary on LABA use in asthma, stating that for maintenance therapy, "LABAs should only be used

as add-on therapy to an anti-inflammatory controller (such as an ICS, ideally, in the same inhaler device) in any age group. If a LABA is used in children, a combination inhaler of an ICS plus a LABA is preferred over separate inhalers of each to preclude the use of a LABA without and ICS, which may arise due to adherence issues."[13]

In fact, in 2011, the British Thoracic Society's asthma guidelines recommended, for the first time, that LABAs should be prescribed in fixed-dose combination ICS/LABA inhalers in the treatment of asthma. This is still the preference in the society's updated 2016 guidelines.[10,14]

This revision was based on the following evidence:

- LABAs have the potential to increase the risk of asthma-related mortality when used by patients with unstable asthma without concomitant ICS therapy or scheduled medical review.[15]
- There is no evidence of increased risk of asthma mortality with combination ICS/LABA therapy.[16]
- Only in combination with ICS/LABA products can it be guaranteed that LABA monotherapy can be avoided.[17]

It is recognized that the use of separate inhalers inevitably results in periods of LABA monotherapy in a proportion of patients, because patients who are poorly adherent to prescribed ICS therapy may continue their LABA inhaler for symptomatic relief.[14,18,19]

Patient preference is an important consideration given the large rates of nonadherence and inhaler misuse, as it has been shown to be positively correlated with inhaler compliance and ultimately better clinical outcomes.[20] In rating the ideal characteristics of a dry powder inhaler (DPI), patients identified the following as the most important characteristics:

- ease of use (both during an attack and in general)
- ability to know how many doses are left
- ease of learning how to use the device. [21]

More specifically, for the different types of DPI devices, randomized, open-label studies evaluating patient preference and satisfaction between multidose and single-dose DPIs have shown that MDPIs are associated with significantly higher patient preference and satisfaction rates than single-dose DPIs.[22] In a recent crossover study, the RespiClick inhaler was found to have higher levels of device mastery, including intuitiveness and ease of use compared with Easyhaler and Turbuhaler.[23]

1.3.2 Place in Therapy

Inhaled medications are the primary treatment for asthma.[24] The Global Initiative for Asthma recommends that treatment with short-acting beta2 agonist monotherapy should be used for patients experiencing asthma symptoms less than twice per month, with no waking due to asthma in the past month, and no risk factors for exacerbations, as well as no severe exacerbations in the previous year.[25] ICS treatment, controller therapy, is then recommended once symptoms exceed this level — not necessarily to reduce the (likely low) burden of symptoms, but to reduce the risk of severe exacerbations. ICS remains the foundation of chronic maintenance pharmacotherapy for asthma patients in all age groups.[12] Failure to achieve acceptable asthma control on low doses of ICS should prompt re-evaluation to identify the cause for lack of response to therapy. This is often due to one of several factors, such as erroneous diagnosis of asthma, poor inhaler device technique, poor adherence to maintenance ICS, ongoing exposure to environmental triggers, and

comorbidities. Thus, controller therapy should only be escalated after reviewing and addressing these factors.[12] This combination is also recommended for "uncontrolled" asthma, which refers to having at least three of the following symptoms in the previous four weeks: daytime asthma symptoms more than twice weekly, any night waking due to asthma, reliever medication needed for symptoms more than twice weekly, and any activity limitation due to asthma.[11,26]

As mentioned earlier, the use of combination ICS/LABA in a single inhaler is preferred to using separate inhalers, according to Canadian and international guidelines, to avoid increased mortality risk and to encourage adherence to prescribed medication.[10-12,27] Recommendations by both the Canadian Thoracic Society and FDA urge the use of combination products containing ICS/LABA in children and adolescents because of the difficulty of ensuring compliance when they are administered separately in these groups, although evidence suggests this benefit could be extended to adults as well.[12,27]

The doses of fluticasone propionate and salmeterol xinafoate in FS MDPI represent lower levels of active drug per inhalation compared with other drugs available for treatment of asthma in Canada. This preparation contains a lower dose than existing fluticasone propionate / salmeterol xinafoate preparations, and pharmacokinetic studies show that the systemic exposure of these products are generally lower than or similar to that of Advair Diskus. Following a single inhalation of 232 mcg/14 mcg FS MDPI, the exposure (maximum plasma-drug concentration and area under the curve) of fluticasone propionate / salmeterol xinafoate was about 20% to 50% lower compared with a 500 mcg/50 mcg dose of Advair Diskus. Of available asthma treatments with the same active ingredients, such as Advair Diskus, FS MDPI contains less active ingredient with 113 mcg/14 mcg or 232 mcg/14 mcg for one inhalation twice daily compared with Advair Diskus with strengths of 100 mcg/50 mcg, 250 mcg/50 mcg, and 500 mcg/50 mcg for one inhalation twice daily and Advair HFA 125 mcg/25 mcg and 250 mcg/25 mcg for two inhalations twice daily.[28] The total daily amounts of each ingredient are shown in Table 2.

Table 2: Total Daily Dose of Fluticasone Propionate and Salmeterol Xinafoate in FS MDPI, Advair Hydrofluoroalkane, and Advair Diskus

Intervention	Total Daily Dose	
	Fluticasone Propionate	**Salmeterol Xinafoate**
FS MDPI	110 mcg to 464 mcg	28 mcg
Advair HFA	500 mcg to 1,000 mcg	100 mcg
Advair Diskus	200 mcg to 1,000 mcg	100 mcg

FS MDPI = fluticasone propionate / salmeterol xinafoate multidose dry powder inhaler; HFA = hydrofluoroalkane.

Source: Clinical study reports.[3-5]

1.3.3 Dosing Considerations

Treatment of asthma for patients with persistent asthma despite treatment with an ICS may be initiated with either ICS and LABA separately, or as a combination ICS/LABA inhaler.[11,12] The most recent update to the Canadian asthma guidelines supported the addition of adjunct therapy with LABA when asthma is not controlled at low or medium doses of ICS. None of the guidelines recommended escalating to high-dose ICS before initiating combination therapy.[12]

The ability to titrate the ICS dose in the combination inhaler allows physicians to adjust treatment to attempt to control asthma symptoms, allowing for increases of ICS without unnecessary dose increases of LABA. Should this approach to control asthma symptoms fail, the remaining options of adding a leukotriene receptor antagonist, anti-immunoglobulin E, and then prednisone are available to patients.[11]

2. Clinical Evidence

To demonstrate the efficacy and safety of fluticasone propionate alone and fluticasone propionate in combination with salmeterol xinafoate, Teva Canada Innovation conducted a full development program consisting of three key phase III studies: two 12-week efficacy and safety studies, which included the usual factorial design to support the efficacy and safety of both the fluticasone propionate mono-component and the fluticasone propionate / salmeterol xinfoate combination product, and a supportive 26-week long-term safety study.

These key phase III clinical trials are detailed further in section 2.1.

2.1 Pivotal Clinical Trials

Three phase III clinical trials were conducted. Two trials, Study 301 and Study 30017, compared FS MDPI with placebo and fluticasone propionate (Fp) multidose dry powder inhaler (in full, Fp MDPI) and one open-label, long-term safety trial, Study 305, compared FS MDPI and fluticasone dipropionate/ salmeterol xinafoate dry powder inhaler (FS DPI) (Advair Diskus). Study 301 and 30017 were efficacy studies that were identical in design (12-week multi-centre, randomized, double-blind, placebo-controlled trials). Study 301 tested 55 mcg/14 mcg and 113 mcg/14 mcg FS MDPI and Study 30017 tested 113 mcg/14 mcg and 232 mcg/14 mcg FS MDPI. Study 305 was a 26-week, randomized, open-label, active drug-controlled safety trial that compared 113 mcg/14 mcg and 232 mcg/14 mcg FS MDPI to 250 mcg/50 mcg and 500 mcg/50 mcg FS DPI.

Table 3: Summary of Pivotal Clinical Studies

Study Name	Design	Objectives	Population
Study 301	12-week, phase III multi-centre, randomized, double-blind, placebo-controlled trial	To evaluate the efficacy of Fp MDPI and FS MDPI	Patients ≥ 12 years of age with persistent asthma who are symptomatic despite low-dose or medium-dose ICS therapy
Study 30017	12-week, phase III multi-centre, randomized, double-blind, placebo-controlled trial	To evaluate the efficacy of Fp MDPI and FS MDPI	Patients ≥ 12 years of age with persistent asthma who are symptomatic despite medium-dose or high-dose ICS therapy
Study 305	26-week, randomized, open-label, active drug-controlled study	To evaluate the long-term safety of Fp MDPI in two strengths and FS MDPI in two strengths, as well as FS DPI in two strengths	Patients with persistent asthma who are currently being treated with medium-dose or high-dose ICS or ICS/LABA as their daily controller

Fp MDPI = fluticasone propionate multidose dry powder inhaler; FS MDPI = fluticasone propionate / salmeterol xinafoate multidose dry powder inhaler; FS DPI = fluticasone propionate / salmeterol xinafoate dry powder inhaler; ICS = inhaled corticosteroid; ICS/LABA = inhaled corticosteroid and long-acting beta2 agonist.

Source: Clinical study reports.[3-5]

2.1.1 Investigational Plan of Pivotal Clinical Trials

A. Trial Characteristics

Study 301 was a 12-week, multi-centre, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of treatment with one inhalation twice a day of FS MDPI 55 mcg/14 mcg or FS MDPI 113 mcg/14 mcg, FP MDPI 55 mcg, and FP MDPI 113 mcg in adolescents and adults with persistent asthma who have previously been treated with low-dose or medium-dose ICS or ICS/LABA therapy.[3]

Study 30017 was a 12-week, multi-centre, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of treatment with one inhalation twice a day of FS MDPI 113 mcg/14 mcg or FS MDPI 232 mcg/14 mcg, FP MDPI 113 mcg, and FP MDPI 232 mcg in adolescents and adults with persistent asthma who have previously been treated with low-dose or medium-dose ICS or ICS/LABA therapy.[4]

Study 305 was an eight-arm, 26-week, multi-centre, randomized, open-label, parallel-group, active-controlled study to evaluate the long-term safety of treatment with either medium- or high-strength ICS monotherapy, or medium- or high-strength ICS/LABA combination therapy, based on the existing asthma regimen of adolescents or adults with persistent asthma who have previously been treated with medium- or high-strength ICS or ICS/LABA therapy. Patients stratified to the medium-strength ICS monotherapy category were randomized 3:1 to receive Fp MDPI 113 mcg twice daily or two puffs of fluticasone propionate hydrofluoroalkane (Fp HFA) (Flovent HFA) 110 mcg twice daily. Patients stratified to 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 additional variables. Patients stratified to the medium-strength ICS/LABA category were randomized 3:1 to FS MDPI 113 mcg/14 mcg twice daily or FS DPI 250 mcg/50 mcg twice daily. Patients stratified to the high-strength ICS/LABA category were randomized 3:1 to FS MDPI 232 mcg/14 mcg twice daily or FS DPI 500 mcg/50 mcg twice daily.[5]

See Table 4 for a further description of Study 301 and Study 30017, and Table 5 for a further description of Study 305. Also refer to the CDR review of Fp MDPI (Aermony RespiClick), as the Fp MDPI arms of these studies were not reported in this review.

Table 4: Details of Included Efficacy Trials

		Study 301	Study 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 the 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[29] • FEV_1 ≥ 40% and ≤ 85% of predicted values for age, height, sex, and race • Diagnosis of asthma ≤ 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[30] • Prior treatment with ICS or ICS/LABA for ≥ 1 month at qualifying dosage (Table 6). If on ICS/LABA, must have pre-screening visit to change to ICS monotherapy and be stable for 1 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 a MDPI device • ≥ 15% reversibility for all patients (and ≥ 200 mL increase for those ≥ 18 years from baseline FEV_1) within 30 minutes following 2 to 4 inhalations of albuterol/salbutamol	
	Exclusion criteria	• History of life-threatening asthma exacerbation • Any of the following prior to 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 2 weeks) • Current smokers, those with a smoking history of ≥ 10 pack years, or those who had used any	

		Study 301	Study 30017
		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/14 mcg b.i.d. • FS MDPI 113 mcg/14 mcg b.i.d.	• Fp MDPI 113 mcg b.i.d. • Fp MDPI 232 mcg b.i.d. • FS MDPI 113 mcg/14 mcg b.i.d. • FS MDPI 232 mcg/14 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	• Change from baseline in weekly average of the trough morning PEF • Asthma symptoms 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[3131312929]	Sher et al., 2016[12,32]

AQLQ(S) = Asthma Quality of Life Questionnaire with Standardized Activities; ATS/ERS = American Thoracic Society / European Respiratory Society Task Force; b.i.d. = twice daily; FEV_1 = forced expiratory volume in one second; FEV_1 $AUC_{0\text{-}12\,h}$ = standardized baseline-adjusted area under the effect curve for forced expiratory volume in one second from zero to 12 hours post dose; Fp MDPI = fluticasone propionate multidose powdered inhaler; FS MDPI = fluticasone propionate / salmeterol xinafoate multidose powdered inhaler; ICS = inhaled corticosteroid; ICS/LABA= inhaled corticosteroid and long-acting beta2 agonist; MDI = metered-dose inhaler; MDPI = multidose powdered inhaler; N = total number in the sample under study; PEF = peak expiratory flow; RCT = randomized controlled trial; SABA = short-acting beta2 agonist.
Source: Clinical study reports,[3,4] Raphael et al., 2017,[31] Sher et al., 2017,[32] and FDA medical and statistical review reports.[33,34]

Table 5: Details of Safety Trial

		Study 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 medium- 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 2 to 4 inhalations of albuterol/salbutamol ○ Diagnosis of asthma present for ≥ 3 months,[29] with no exacerbations or changes in medications for at least 1 month • Ability to perform repeatable spirometry consistent with ATS/ERS 2005 criteria[30] • 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 prior to 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

		Study 305
		• Bacterial or viral infection of the upper or lower respiratory tract, sinus, or middle ear (within 2 weeks) • Current smokers, those with a smoking history of ≥ 10 pack years, or those who 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/14 mcg b.i.d. • FS MDPI 232 mcg/14 mcg b.i.d.
	Comparators	• Fp HFA 110 mcg b.i.d. • Fp HFA 220 mcg b.i.d. • FS DPI 250 mcg/50 mcg b.i.d. • FS DPI 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 • Withdrawals due to worsening asthma • Asthma symptoms scores • Health care resource utilization • Antibiotic usage
NOTES	**Publications**	Mansfield et al., 2017

AQLQ(S) = Asthma Quality of Life Questionnaire with Standardized Activities; ATS/ERS = American Thoracic Society / European Respiratory Society Task Force; b.i.d. = twice daily; FEV_1 = forced expiratory volume in one second; FEV_1 $AUC_{0\text{-}12\ h}$ = standardized baseline-adjusted area under the effect curve forced expiratory volume in one second from zero to 12 hours post dose; Fp HFA = fluticasone propionate hydrofluoroalkane; Fp MDPI = fluticasone propionate multidose dry powder inhaler; FS DPI = fluticasone propionate / salmeterol xinafoate dry powder inhaler; FS MDPI = fluticasone propionate / salmeterol xinafoate multidose dry powder inhaler; ICS = inhaled corticosteroid; ICS/LABA = inhaled corticosteroid and long-acting beta2 agonist; MDI = metered-dose inhaler; N = total number in the sample under study; RCT = randomized controlled trial; SABA= short-acting beta2 agonist.

Source: Clinical study report,[5] Mansfield et al., 2017,[35] and FDA medical and statistical review reports.[33,34]

Populations

Efficacy Trials

Screening eligibility criteria was similar in both Study 301 and Study 30017, with the exception of the qualifying therapies of treatment. Study 301 aimed to include patients taking low- or medium-dose ICS monotherapy or an 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) at least 40% and less than or equal to 85% of predicted values for age height, sex and race; and also 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). It was also required that a patient have a diagnosis of asthma as defined by the National Institutes of Health,[29] that the diagnosis be present for a minimum of

three months, and that the patient have had no exacerbations and no changes in asthma medication for at least 30 days before 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 or 160 mcg/dosage)	80 to 480	> 160
Budesonide HFA (100 mcg or 200 mcg/dosage)	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

DPI = dry powder inhaler; HFA = hydrofluoroalkane; ICS = inhaled corticosteroid; ICS/LABA = inhaled corticosteroid and long-acting beta2 agonist; MDI = metered-dose inhaler; pMDI = pressurized metered-dose inhaler.

Source = Clinical study reports.[3,4]

Safety Trial

Patients were included in Study 305 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 ≥ 40% of the value predicted for age, height, sex, and race, and unlike the efficacy studies, Study 301 and Study 30017, did not specify an upper limit for FEV_1. Patients were required to have a treatment regimen that included a short-acting beta2 agonist (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-strength ICS treatment arm. All patients were required to have been maintained on a stable dose of ICS or ICS/LABA for four weeks prior to the screening visit at one of the qualifying dosages summarized in Table 7. Lastly, patients were required to demonstrate a ≥ 12% reversibility of FEV_1 (and 200 mL for patients aged 18 years and older) within 30 minutes following four inhalations of salbutamol hydrofluoroalkane (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 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; HFA = hydrofluoroalkane; ICS= inhaled corticosteroid; ICS/LABA= inhaled corticosteroid and long-acting beta2 agonist; pMDI = pressurized metered-dose inhaler.

Source: Clinical study reports.[5]

Intervention

FS MDPI is an inhalation-driven MDPI containing fluticasone propionate and salmeterol xinafoate dispersed in a lactose monohydrate excipient and contained within a reservoir. A metered dose is delivered to a dose cup via an air pulse that is activated when the cap is opened. The dose is delivered to the patient through a cyclonic separator activated by patient inhalation. The cyclonic action of the device delivers fine particles of the drug to the small airways of the lungs while the larger excipient particles are deposited in the throat and mouth. The inhaler contains 60 actuations.

In Study 301, the interventions were FS MDPI 55 mcg/14 mcg for one inhalation twice daily or FS MDPI 113 mcg/14 mcg for one inhalation twice daily. Intervention groups in both Study 30017 and Study 305 included FS MDPI 113 mcg/14 mcg for one inhalation twice daily or FS MDPI 232 mcg/14 mcg for one inhalation twice daily treatment arms.

Comparators

Efficacy Trials (Study 301 and Study 30017)

The comparators in Study 301 and Study 30017 included Fp MDPI, which is an identical MPDI containing only Fp. This inhaler also contains 60 actuations. The placebo, manufactured by Teva Canada Innovation, was supplied in a MDPI device that was identical to the devices used to deliver active drug, and was indistinguishable from the active treatments. Patients taking these products were instructed to take one inhalation twice daily. In both efficacy studies, all treatments were administered as one inhalation twice daily for 12 weeks +/- two days.

During the 14- to 21-day run-in period, all patients discontinued their current ICS therapy and were administered the following treatments: one inhalation of single-blinded Fp MDPI 55 mcg twice per 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 40 mcg HFA metered-dose inhaler or equivalent (Study 301). In both trials, patients were provided with albuterol/salbutamol HFA metered-dose inhaler to replace their current rescue medication, to be used on an as-needed basis. 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 8.

Table 8: Prohibited Medications During Study 301 and Study 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 agents	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., anti–tumour necrosis factor alpha drugs)	90 days
Immunosuppressive therapy (e.g., methotrexate)	30 days
Immunotherapy[c]	Initiation within 90 days, 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
Intranasal aerosol corticosteroids[d]	Discontinue at SV
Leukotriene modifiers	7 days
Monoamine oxidase inhibitors	14 days
Oral beta2 agonists (tablets, syrup)	7 days
Oral or nasal antihistamines (e.g., loratadine, diphenhydramine, cetirizine)	Discontinue 24 hours before SV, RV, and 9 of 10 TVs, and resume use after completion of the visit
Strong CYP3A4 inhibitors (e.g., 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

Type of Medication	Washout Period Before the Screening Visit (Unless Otherwise Specified)
Electronic cigarettes	Discontinue 24 hours before the SV and discontinue upon entering run-in
Tricyclic antidepressants	14 days

CYP3A4 = cytochrome P450 3A4; LABA = long-acting beta2 agonist; RV = randomization visit; SV = screening visit; TV = treatment visit.

[a] Chronic stable dosages of acetylsalicylic acid (no more than 325 mg/day) for cardiovascular prophylaxis are allowed.
[b] Chronic stable dosages of ocular steroids of at least seven 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 dosages of aqueous intranasal corticosteroids of at least seven 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 dosages 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.[3,4]

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 and 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. Adherence to treatment during these studies was assessed based on data collected in the MDPI's dose counter and the patient's diary.

Safety Trial (Study 305)

The comparator in Study 305 was FS DPI 250 mcg/50 mcg, which is a dry powder formulation of Fp 250 mcg and 50 mcg of salmeterol base in a lactose excipient, and FS DPI 500 mcg /50 mcg, which contains 500 mcg of Fp and 50 mcg of salmeterol base. Patients taking this product were instructed to take one inhalation twice daily, which provided a daily dose of fluticasone propionate/ salmeterol xinafoate 500 mcg/100 mcg and 1,000 mcg/100 mcg for a 26-week duration.

During the 14- to 21-day 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 medication with salbutamol (or albuterol) HFA. Concomitant medication use was monitored and recorded throughout the study. The medications listed in Table 9 were to be discontinued for specified times leading up to the screening visit and prohibited for the length of the trial. The list of prohibited medications in this trial differed from those in Study 301 and Study 30017 in that ICS or LABA therapy were discontinued upon randomization and allowed during the run-in period, and leukotriene modifiers were permitted to be used leading up to and throughout the study.

Table 9: 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 agents	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., anti–tumour necrosis factor alpha drugs)	90 days
Immunosuppressive therapy (e.g., methotrexate)	30 days
Immunotherapy[c]	Initiation within 90 days, 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 beta2 agonists (tablets, syrup)	7 days
Oral or nasal antihistamines (e.g., loratadine, diphenhydramine, cetirizine)	Discontinue 24 hours before SV, RV, and 9 of 10 TVs, and resume use after completion of the visit
Strong CYP3A4 inhibitors (e.g., 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

CYP3A4 = cytochrome P450 3A4; LABA = long-acting beta2 agonists; RV = randomization visit; SV = screening visit; TV = treatment visits.

[a] Chronic stable dosages of acetylsalicylic acid (no more than 325 mg/day) for cardiovascular prophylaxis are allowed.
[b] Chronic stable dosages of ocular steroids of at least seven days' duration, with dosages 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 dosage for 30 days or more before the SV. The patient must remain on this stable regimen throughout the study.
[d] Chronic stable dosages of aqueous intranasal corticosteroids of at least seven 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 dosages 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.[5]

Study drug training on the inhaler devices was provided at every visit, from the randomization visit until the penultimate treatment visit (week 22). Study adherence was checked during all visits beginning at the randomization visit and 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 this study was assessed based on data collected in the device's dose counter and the patient's diary.

Outcomes

Efficacy Trials (Study 301 and Study 30017)

The primary efficacy measures and variables for Study 301 and Study 30017 were as follows:

- change from baseline in trough (morning pre-dose and pre-rescue bronchodilator) FEV_1 at week 12
- standardized baseline-adjusted area under the effect curve for forced expiratory volume in one second from zero to 12 hours post dose (FEV_1 $AUEC_{0\text{-}12\,h}$) at week 12, analyzed for the subset of approximately 300 patients who performed post-dose serial spirometry.

The secondary outcomes in Study 301 and Study 30017 were as follows:

- change from baseline in weekly average of daily trough morning peak expiratory flow (PEF) over the 12-week treatment period
- change from baseline in weekly average of total daily asthma symptoms scores 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 Asthma Quality of Life Questionnaire (Standardised) (AQLQ[S]) (patients ≥ 18 years of age only) at end point.

Safety was assessed by qualified investigational centre personnel monitoring physical examinations, oropharyngeal examinations, 12-lead electrocardiograms, vital signs, concomitant medication usage, and adverse events (AEs).

Safety Trial (Study 305)

Study 305 evaluated safety, with the primary outcome measure of incidence and type of AEs for the two strengths of FS MDPI. Severity of AEs was recorded as either mild (no limitation of usual activities), moderate (some limitation of usual activities), or severe (inability to carry out usual activities). The secondary objective of this study was to evaluate the safety of FS MDPI in comparison with FS DPI. The incidence of adverse reactions with FS MDPI was also reported in Study 301 and Study 30017 as a secondary patient-reported outcome.

Study 305 had a reasonable power to detect a change from baseline in trough FEV_1 over 26 weeks, 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 FS MDPI and FS DPI at a 0.025 1-sided significance level.

Statistical Analyses

Primary Efficacy Analyses

The sample size and power in Study 301 were calculated to demonstrate superiority of Fp MDPI 55 mcg twice daily over placebo in change from baseline in trough FEV_1 at week 12, as well as superiority of FS MDPI 55 mcg/14 mcg twice daily over Fp MDPI 55 mcg twice daily in standardized baseline-adjusted FEV_1 $AUEC_{0\text{-}12h}$ at week 12. In Study 30017, the sample size and power were calculated to demonstrate a superiority of Fp MDPI 113 mcg twice daily over placebo in change from baseline in trough FEV_1 at week 12, and the superiority of FS MDPI 113 mcg/14 mcg twice daily over Fp MDPI 113 mcg twice daily in

standardized baseline-adjusted FEV_1 $AUEC_{0\text{-}12h}$ at week 12. Safety was the primary objective of Study 305, and the determination of sample size for the safety analysis was not based on statistical considerations.

Change from baseline in trough FEV_1 at week 12 was the primary outcome for Study 301 and Study 30017. The analysis was performed using an analysis of covariance (ANCOVA) model that included baseline trough FEV_1, sex, age, (pooled) centre, previous therapy (ICS or ICS/LABA), and treatment as covariates. A co-primary outcome in Study 301 and Study 30017 was change from baseline-adjusted FEV_1 $AUEC_{0\text{-}12\,h}$ at week 12, based on actual time of measurement. It was calculated as post-dose FEV_1 after subtracting the baseline FEV_1 value, and performed using an ANCOVA model with fixed effects of treatment, sex, (pooled) centre, and previous therapy (ICS or ICS/LABA), and with covariates of age and baseline FEV_1.

For the noninferiority assessment of change from baseline in trough FEV_1 over 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 −0.125 L, and 240 patients in the FS 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 1-sided noninferiority comparison.

The treatment effect and variability assumptions for power calculations in Study 301 and Study 30017 were based on data collected in Teva Canada Innovation studies. The treatment effect and variability assumptions in Study 305 were based on results from a previous phase II trial, Study 201.[28]

Secondary Efficacy Analyses

If all inferential comparisons in the primary analysis were significant (Table 10), then inferential testing was extended to the secondary analysis in a sequential manner in accordance with a fixed-sequence multiple testing procedure (Table 11).

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

Albuterol/salbutamol daily use: The 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 was analyzed using a 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 the weekly average 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 during the 12-week treatment period was analyzed over weeks 1 to 12 in Study 301 and Study 30017 using a logistic regression model that included sex, age, (pooled) centre, previous therapy (ICS or ICS/LABA), and treatment as covariates.

The time to first severe asthma exacerbation was an outcome in Study 305, and was calculated from the date of the first dosage 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. The median time to first severe asthma exacerbation and associated 95% confidence intervals (CIs) were estimated as appropriate.

AQLQ(S) (18+): In Study 301 and Study 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 of age at the 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 via last-observation carried forward. In the statistical analysis plan for these trials, a combined single end point of AQLQ(S) and the Standardised Paediatric Asthma Quality of Life Questionnaire 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 the Paediatric Asthma Quality of Life Questionnaire for patients aged 12 to 17 years of age 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 Study 301 and Study 30017, the change from baseline in the percentage of 24-hour periods with no use of rescue medication as recorded in the morning and evening patient diaries during the 12-week treatment period was compared between treatment arms using the Wilcoxon-Mann-Whitney test. Also in these studies, the change from baseline in the percentage of symptom-free 24-hour periods (defined as 24-hour periods with asthma symptoms scores of zero) as recorded in patient diaries during the 12-week treatment period was also compared between treatment arms using the Wilcoxon-Mann-Whitney test. In the safety study, 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 Study 301 and Study 30017, the change from baseline in the percentage of asthma-controlled 24-hour periods (defined as 24 hours periods with asthma symptoms scores of zero and no rescue medication use) during the 12-week treatment period was summarized and compared between treatment arms using the Wilcoxon-Mann-Whitney test.

Multiple Comparisons

Efficacy Trials (Study 301 and Study 30017)

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 (2-sided). In Study 301 and Study 30017, the testing sequence began with four tests involving FEV_1 $AUEC_{0\text{-}12\ h}$ at 12 weeks followed by four tests involving trough FEV_1 at 12 weeks. As shown in Table 10, 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 $AUEC_{0\text{-}12\ h}$ at 12 weeks, followed by comparisons between the FS MDPI formulations and placebo for FEV_1 $AUEC_{0\text{-}12\ h}$ at 12 weeks. For trough FEV_1, each of the active treatment

groups was 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 10: Statistical Testing Hierarchy for Primary End Points in Efficacy Trials

Study	End Point	Comparison	Sequence
301	FEV_1 $AUEC_{0\text{-}12\ h}$ at 12 weeks[a]	FS MDPI 113 mcg/14 mcg b.i.d. vs. Fp MDPI 113 mcg b.i.d.	1
		FS MDPI 55 mcg/14 mcg b.i.d. vs. Fp MDPI 55 mcg b.i.d.	2
		FS MDPI 113 mcg/14 mcg b.i.d. vs. placebo	3
		FS MDPI 55 mcg/14 mcg b.i.d. vs. placebo	4
	Trough FEV_1 at 12 weeks	FS MDPI 113 mcg/14 mcg b.i.d. vs. placebo	5
		FS MDPI 55 mcg/14 mcg b.i.d. vs. placebo	6
		Fp MDPI 113 mcg b.i.d. vs. placebo	7
		Fp MDPI 55 mcg b.i.d. vs. placebo	8
30017	FEV_1 $AUEC_{0\text{-}12\ h}$ at 12 weeks[a]	FS MDPI 232 mcg/14 mcg b.i.d. vs. Fp MDPI 232 mcg b.i.d.	1
		FS MDPI 113 mcg/14 mcg b.i.d. vs. Fp MDPI 113 mcg b.i.d.	2
		FS MDPI 232 mcg/14 mcg b.i.d. vs. placebo	3
		FS MDPI 113 mcg/14 mcg b.i.d. vs. placebo	4
	Trough FEV_1 at 12 weeks	FS MDPI 232 mcg/14 mcg b.i.d. vs. placebo	5
		FS MDPI 113 mcg/14 mcg b.i.d. vs. placebo	6
		Fp MDPI 232 mcg b.i.d. vs. placebo	7
		Fp MDPI 113 mcg b.i.d. vs. placebo	8

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

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

Source: Clinical study reports.[3,4]

According to the statistical analysis plan for Study 301 and Study 30017, if all primary comparisons were statistically significant at the probability (*P*) < 0.05 level, an inferential testing procedure would subsequently be performed for the secondary efficacy end points for FS MDPI at dosage strengths used in their respective study (Table 11).[3,4] This process was to continue testing sequentially through each FS 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 type I error within each end point (or row), or each dose comparison over placebo (or column). It did not, however, control the overall type I error.

Table 11: Statistical Testing Hierarchy for Secondary End Points in Efficacy Trials

Secondary End Point	Hypothesis Testing									
	Study 301					Study 30017				
	FS MDPI 113 mcg/ 14 mcg vs. Placebo	FS MDPI 55 mcg/ 14 mcg vs. Placebo	FS MDPI 113 mcg/ 14 mcg vs. Fp MDPI 113 mcg	FS MDPI 55 mcg/ 14 mcg vs. Fp MDPI 55 mcg	FS MDPI 55 mcg/ 14 mcg vs. Fp MDPI 113 mcg	FS MDPI 232 mcg/ 14 mcg vs. Placebo	FS MDPI 113 mcg/ 14 mcg vs. Placebo	FS MDPI 232 mcg/ 14 mcg vs. Fp MDPI 232 mcg	FS MDPI 113 mcg/ 14 mcg vs. Fp MDPI 113 mcg	FS MDPI 113 mcg/ 14 mcg vs. Fp MDPI 232 mcg
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 symptoms 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 Standardised Activities); Fp MDPI = fluticasone propionate multidose dry powder inhaler; FS MDPI= fluticasone propionate / salmeterol xinafoate multidose dry powder inhaler; *P* = probability; PEF = peak expiratory flow; vs. = versus.

Note: Arrows indicate the direction of the sequence in which comparisons were made to placebo. This process tested sequentially through the next FS MDPI strength until either all comparisons were made or 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. Fp MDPI comparisons were tested separately.

Source: Clinical study reports.[3,4]

All primary end point comparisons specified in the fixed-sequence multiple testing procedure were found to be statistically significant in Study 301 and Study 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 11). The comparison for the first secondary end point in the hierarchy, a 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.

Safety Trial

In the open-label safety study, 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 12. The two efficacy trials used a full analysis set for evaluating the efficacy end points, with intention-to-treat (ITT) and per-protocol data sets conducted as supportive analyses.

Table 12: Analysis Populations From the Included Studies

Analysis Set	Description
Efficacy Trials (Study 301 and Study 30017)	
ITT population	This included all randomized patients. The ITT population was used in supportive efficacy analyses.
FAS population	This included all patients in the ITT population who received at least 1 dosage of the post-randomization study treatments and had at least 1 post-baseline trough FEV_1 assessment. The FAS was used for the primary analyses of the efficacy end points.
PP population	This included all data from randomized patients prior to experiencing a major protocol violation. These were patients 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	This included all randomized patients who received at least 1 dosage of the study drug. The safety population was used for all analyses of safety data.
Serial spirometry subset	These were patients who were enrolled at 1 of the investigational centres selected 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 $AUEC_{0\text{-}12h}$, a co-primary end point of Study 301 and Study 30017.
Safety Trial (Study 305)	
Safety population	This included all randomized patients who received at least 1 dosage of the randomized study treatments. The safety population was used for all analyses of safety data.
ITT population	This included all randomized patients.
FAS population	This included all patients in the ITT population who received at least 1 dosage of the study treatments and had at least 1 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 $AUC_{0\text{-}12h}$ = standardized baseline-adjusted area under the effect curve for forced expiratory volume in one second from zero to 12 hours post dose; ITT = intention-to-treat; PP = per-protocol.

Source: Clinical study reports.[3-5]

Missing Data

Efficacy Analyses in Efficacy Trials (Study 301 and Study 30017)

For the primary end point of change from baseline in trough FEV_1 at week 12, missing data caused by early dropout from Study 301 and Study 30017 were handled by penalizing the positive change from baseline in trough FEV_1 score using a baseline-observation carried forward method. This method assigned patients who had withdrawn early a change from baseline in trough FEV_1 score of zero; therefore, the discontinued patients would be treated as failures. Discontinued patients with a negative change from baseline in FEV_1 did not have their results adjusted by this method. No adjustments were made to results for patients who had completed the study. For the MMRM, there was no imputation for missing data. Missing data for secondary outcomes were imputed via last-observation carried forward.

Analyses in Safety Trial (Study 305)

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, Study 301 and Study 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 (Study 301 and Study 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 a 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 non-missing 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 analyzed 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 model that included baseline FEV_1, sex, age, (pooled) centre, previous therapy (ICS or ICS/LABA), and treatment as covariates, imputing missing data using last-observation carried forward.

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 to 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 arm, the missing FEV_1 values were imputed based on measurements observed at previous visits and treatment arms, and were assumed to be missing at random. For the active treatment arms, 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 the missing-at-random value); it was subsequently increased and the process repeated until the treatment effect became no longer significant at the 5% level. The shift point at which the effect was no longer significant was the tipping point.

B. Results

Baseline Characteristics

In Study 301, the treatment arms were similar with regard to age, sex, race, and body mass index. All patients enrolled in the study were required to have persistent asthma. Baseline spirometry results were generally similar between treatment arms (the mean FEV_1 ranged from 2.162 L to 2.302 L). Other characteristics, such as the proportion of previous smokers or proportion of patients whose previous treatment included an ICS/LABA, were also similar.

In Study 30017, the treatment arms were well-matched with regard to demographic and baseline characteristics for all populations. All patients enrolled in the study were required to have persistent asthma. Baseline spirometry results were generally similar between patients across treatment arms; the mean FEV_1 ranged from 2.069 L to 2.157 L.

Approximately two-thirds of patients in both Study 301 and Study 30017 used at least one concomitant medication during the study, with no notable difference between placebo and active treatments in concomitant medication use. Medication therapeutic classes reported for at least 10% of patients overall in either study were the following:

- antihistamines for systemic use (115 patients [18%] in Study 301, 189 patients [26%] in Study 30017)
- agents acting on the renin-angiotensin system (100 patients [16%] in Study 301, 132 patients [18%] in Study 30017)
- analgesics (93 patients [15%] in Study 301, 154 patients [21%] in Study 30017)
- nasal preparations (73 patients [11%] in Study 301, 129 patients [18%] in Study 30017)
- lipid-modifying agents (65 patients [10%] in Study 301)
- vitamins (88 patients [12%] in Study 30017)
- sex hormones and modulators of the genital system (84 patients [12%] in Study 30017)
- drugs for acid-related disorders (80 patients [11%] in Study 30017)
- antibacterials for systemic use (70 patients [10%] in Study 30017).

Baseline characteristics for the Fp MDPI treatment groups in Study 301 and Study 30017 are presented in the clinical review report for Aermony RespiClick.

Table 13: Summary of Baseline Characteristics for Efficacy Trials

Baseline Characteristics		Study 301			Study 30017		
		Placebo (N = 130)	FS MDPI 55 mcg/ 14 mcg b.i.d. (N = 129)	FS MDPI 113 mcg/ 14 mcg b.i.d. (N = 130)	Placebo (N = 145)	FS MDPI 113 mcg/ 14 mcg b.i.d. (N = 145)	FS MDPI 232 mcg/ 14 mcg b.i.d. (N = 146)
Age (Years)	Mean (SD)	40.9 (17.35)	41.4 (18.61)	41.0 (17.00)	44.5 (16.05)	44.3 (14.88)	44.7 (16.93)
	12 to 17 years, n (%)	17 (13)	19 (15)	19 (15)	6 (4)	8 (6)	12 (8)
	18 to 64 years, n (%)	102 (78)	97 (75)	100 (78)	125 (86)	125 (86)	115 (79)
	65+ years, n (%)	11 (8)	13 (10)	10 (8)	14 (10)	12 (8)	19 (13)
Sex, n (%)	Male	60 (46)	58 (45)	57 (44)	54 (37)	66 (46)	59 (40)
	Female	70 (54)	71 (55)	72 (56)	91 (63)	79 (54)	87 (60)
Race, n (%)	White	101 (78)	93 (72)	109 (84)	124 (86)	112 (77)	125 (86)
	African American	26 (20)	19 (15)	20 (16)	18 (12)	28 (19)	20 (14)
	Asian	1 (< 1)	1 (< 1)	4 (3)	2 (1)	0	0
	American Indian or Alaska Native	0	0	0	0	0	0
	Other	2 (2)	0	0	1 (< 1)	5 (3)	1 (< 1)
BMI (kg/m^2)	Mean (SD)	27.99 (6.849)	28.00 (7.166)	27.94 (6.686)	29.3 (7.45)	30.2 (7.60)	29.4 (7.35)
Duration of asthma, n (%)	3 to < 6 months	1 (< 1)	0	3 (2)	0	0	0
	6 months to < 1 year	2 (2)	5 (4)	0	4 (3)	4 (3)	0
	1 to < 5 years	12 (9)	15 (12)	20 (16)	13 (9)	14 (10)	18 (12)
	5 to < 10 years	32 (25)	20 (16)	28 (22)	23 (16)	16 (11)	21 (14)
	10 to < 15 years	22 (17)	26 (20)	19 (15)	22 (15)	29 (20)	22 (15)
	15 years or longer	61 (47)	63 (49)	59 (46)	83 (57)	82 (57)	85 (58)
History of smoking	Prior smoker	12 (9)	13 (10)	18 (14)	23 (16)	28 (19)	20 (14)
	No tobacco use	118 (91)	116 (90)	111 (86)	122 (84)	117 (81)	126 (86)
Number of pack Years	n	12	12	18	23	28	20
	Mean (SD)	3.7 (2.82)	2.8 (2.46)	4.3 (3.26)	4.1 (2.80)	3.2 (3.01)	2.9 (2.67)
	Median (min., max.)	3.5 (0.5, 9.0)	2.5 (0.1, 7.0)	4.5 (0.4, 9.5)	4.2	3.9	5.0
Previous therapy	ICS	102 (78)	90 (70)	97 (75)	68 (47)	67 (46)	73 (50)
	ICS/LABA	28 (22)	39 (30)	32 (25)	77 (53)	78 (54)	73 (50)
FEV_1 (L)	Mean (SD)	2.188	2.302	2.162	2.141	2.157	2.083

Baseline Characteristics		Study 301			Study 30017		
		Placebo (N = 130)	FS MDPI 55 mcg/ 14 mcg b.i.d. (N = 129)	FS MDPI 113 mcg/ 14 mcg b.i.d. (N = 130)	Placebo (N = 145)	FS MDPI 113 mcg/ 14 mcg b.i.d. (N = 145)	FS MDPI 232 mcg/ 14 mcg b.i.d. (N = 146)
		(0.5628)	(0.6526)	(0.5522)	(0.6849)	(0.6402)	(0.6532)
	Median (min., max.)	2.095 (0.980, 3.910)	2.238 (1.015, 3.870)	2.133 (1.090, 3.760)	1.975 (0.765, 3.860)	2.060 (1.050, 3.995)	1.940 (0.840, 3.740)
FVC (L)	Mean (SD)	3.282 (0.9005)	3.370 (0.9367)	3.180 (0.8627)	3.210 (0.9745)	3.344 (0.9366)	3.224 (0.9972)
	Median (min., max.)	3.110 (1.400, 5.925)	3.370 (1.370, 6.265)	3.040 (1.405, 6.075)	3.040 (1.330, 5.755)	3.118 (1.715, 6.595)	3.080 (1.320, 6.650)
FEF_{25-75} (L/sec)	Mean (SD)	1.464 (0.6337)	1.687 (0.8363)	1.476 (0.5769)	1.417 (0.7319)	1.355 (0.6976)	1.324 (0.6962)
	Median (min., max.)	1.410	1.655 (0.275, 5.195)	1.353 (0.430, 3.075)	1.260 (0.355, 4.135)	1.240 (0.23, 3.575)	1.150 (0.310, 3.575)
FEV_1/FVC (%)	Mean (SD)	67.611 (9.7695)	69.083 (11.6510)	68.943 (9.5317)	67.090 (9.9384)	64.913 (9.8427)	65.293 (10.4326)
	Median (min., max.)	67.550	69.875 (40.250, 95.800)	69.725 (44.650, 95.400)	67.025 (38.00, 90.25)	65.300 (41.50, 87.55)	65.000 (40.30, 93.20)
% of predicted FEV_1	Mean (SD)	66.96 (11.194)	69.71 (10.873)	67.11 (11.224)	65.55 (10.747)	65.46 (10.852)	64.72 (11.226)
	Median (min., max.)	69.50 (41.00, 83.50)	72.00 (41.00, 85.00)	69.50 (41.50, 92.00)	66.00 (41.50, 84.50)	67.00 (41.00, 85.00)	66.00 (40.00, 85.50)
Asthma medication reported at screening,[a] n (%)	Salbutamol	113 (87)	99 (77)	115 (89)	125 (86)	121 (83)	126 (86)
	Fluticasone propionate	48 (37)	53 (41)	55 (43)	53 (37)	59 (41)	66 (45)
	Beclo-methasone dipropionate	31 (24)	28 (22)	33 (26)	12 (8)	17 (12)	13 (9)
	Budesonide	28 (22)	28 (22)	23 (18)	44 (30)	49 (34)	32 (22)
	Fluticasone propionate and salmeterol xinafoate (Seretide)	19 (15)	25 (19)	27 (21)	37 (26)	40 (28)	47 (32)
	Salbutamol sulphate	15 (12)	18 (14)	11 (9)	17 (12)	20 (14)	13 (9)
	Budesonide with formoterol fumarate	10 (8)	12 (9)	5 (4)	23 (16)	24 (17)	16 (11)
	Mometasone furoate and formoterol fumarate	2 (2)	3 (2)	2 (2)	13 (9)	7 (5)	13 (9)

Baseline Characteristics		Study 301			Study 30017		
		Placebo (N = 130)	FS MDPI 55 mcg/ 14 mcg b.i.d. (N = 129)	FS MDPI 113 mcg/ 14 mcg b.i.d. (N = 130)	Placebo (N = 145)	FS MDPI 113 mcg/ 14 mcg b.i.d. (N = 145)	FS MDPI 232 mcg/ 14 mcg b.i.d. (N = 146)
	(Dulera)						
	Mometasone furoate	8 (6)	4 (3)	8 (6)	14 (10)	7 (5)	15 (10)
	Ciclesonide	4 (3)	4 (3)	5 (4)	15 (10)	5 (3)	9 (6)
	Montelukast	7 (5)	7 (5)	4 (3)	3 (2)	7 (5)	3 (2)

b.i.d. = twice daily; 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; FS MDPI= fluticasone propionate / salmeterol xinafoate multidose dry powder inhaler; FVC = force vital capacity; ICS = inhaled corticosteroid; ICS/LABA = inhaled corticosteroid and long-acting beta2 agonist; min. = minimum; max. = maximum; n = number of patients with characteristic; N = total number of patients; SD = standard deviation.

[a] Prior medications are all medications taken prior to the first day of study medication during the treatment period. Patients were discontinued on all asthma medication included in Table 13 during the run-in period, with the exception of montelukast.

Source: Clinical study reports.[3,4]

Safety Trial

Table 14 provides a summary of key baseline characteristics for the ICS/LABA 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 FS DPI 500 mcg/50 mcg arm containing the largest proportion of these patients (93%) relative to the other arms (76% to 80%). The proportion of females was higher in the FS MDPI 113 mcg/14 mcg arm (70%) compared with other arms (49% to 54%).

Between the medium-strength ICS/LABA categories, the 113 mcg/14 mcg FS MDPI arm had a higher mean FEV_1 at baseline compared with those in the FS DPI 250 mcg/50 mcg arm (2.54 L versus 2.44 L, respectively). There were also more patients in the FS MDPI 113 mcg/14 mcg category who had asthma for less than five years (5%) compared with patients in the FS DPI 250 mcg/50 mcg arm (zero), and a slightly lower median age in the FS MDPI 113 mcg/14 mcg arm (46.0 years) compared with the FS DPI 250 mcg/50 mcg arm (52.0 years).

Within the medium-strength ICS cohort, there were no patients in the FS MDPI 113 mcg/14 mcg arm who were concomitantly using montelukast, compared with 5% in the FS DPI 250 mcg/50 mcg arm. Within the high-strength ICS cohort, 2% of patients in the FS MDPI 232 mcg/14 mcg arm were taking montelukast, compared with none in the FS DPI 500 mcg/50 mcg arm.

Between the high-strength ICS categories, the FS MDPI 232 mcg/14 mcg arm had a higher proportion of patients who were 12 to 17 years of age (7%) than patients in the FS DPI 500 mcg/50 mcg arm (2%). There was also a higher proportion of patients who were 65 years of age or greater in the FS MDPI 232 mcg/14 mcg arm (14%) compared with the FS DPI 500 mcg/50 mcg arm (5%). Regardless, the mean age of both groups appeared to be similar. Likewise, there was a higher proportion of patients with a duration of asthma under one year in the FS MDPI 232 mcg/14 mcg arm (2%) compared with none in the FS DPI 500 mcg/50 mcg arm, as well as a higher proportion of patients 65 years of age or greater in the FS MDPI 232 mcg/14 mcg arm (13%) compared with those in the FS DPI 500 mcg/50 mcg arm (9%).

Baseline characteristics for the Fp MDPI treatment groups in Study 305 are presented in the clinical review report for Aermony RespiClick.

Table 14: Summary of Baseline Characteristics for Safety Trial

Baseline Characteristics		Medium-Strength ICS		High-Strength ICS	
		FS MDPI 113 mcg/ 14 mcg b.i.d. (N = 120)	FS DPI 250 mcg/50 mcg b.i.d. (N = 41)	FS MDPI 232 mcg/ 14 mcg b.i.d. (N = 133)	FS DPI 500 mcg /50 mcg b.i.d. (N = 44)
Age (Years)	Mean (SD)	43.9 (17.58)	45.9 (17.22)	46.1 (16.00)	45.6 (13.92)
	Median (range)	46.0 (12.0, 78.0)	52.0 (13.0, 69.0)	48.0 (12.0, 76.0)	48.5 (14.0, 79.0)
	12 to 17 years	13 (11)	5 (12)	9 (7)	1 (2)
	18 to 64 years	94 (78)	31 (76)	106 (80)	41 (93)
	65+ years	13 (11)	5 (12)	18 (14)	2 (5)
	Missing	0	0	0	0
Ethnicity, n (%)	Not Hispanic/Latino	99 (83)	36 (88)	112 (84)	39 (89)
	Hispanic/Latino	21 (18)	5 (12)	20 (15)	5 (11)
	Unknown	0	0	1 (< 1)	0
	Missing	0	0	0	0
Race, n (%)	White	99 (83)	32 (78)	95 (71)	31 (70)
	African American	19 (16)	9 (22)	31 (23)	12 (27)
	Asian	2 (2)	0	4 (3)	0
	American Indian or Alaska Native	0	0	2 (2)	0
	Pacific Islander	0	0	0	1 (2)
	Other	0	0	1 (< 1)	0
	Missing	0	0	0	0
Sex, n (%)	Male	36 (30)	21 (51)	61 (46)	21 (48)
	Female	84 (70)	20 (49)	72 (54)	23 (52)
	Missing	0	0	0	0
Weight (kg)	Mean (SD)	83.9 (22.48)	82.7 (22.18)	85.7 (19.39)	92.1 (22.80)
	Median (range)	80.3 (34.9, 181.4)	81.6 (36.3, 134.3)	83.9 (47.2, 143.3)	86.6 (59.0, 142.9)
Height (cm)	Mean (SD)	167.2 (10.54)	168.8 (9.16)	167.1 (9.74)	169.3 (10.85)
	Median (range)	165.1 (149.1, 192.7)	170.0 (149.9, 188.0)	166.2 (146.5, 198.1)	168.3 (149.9, 203.2)
BMI (kg/m^2)	Mean (SD)	30.0 (7.85)	28.9 (7.14)	30.7 (7.18)	32.0 (6.68)
	Median (range)	28.9 (14.5, 69.7)	28.1 (16.2, 43.6)	29.6 (17.5, 56.7)	32.1 (21.7, 49.3)
FEV_1 (L)	Mean (SD)	2.54 (0.869)	2.44 (0.696)	2.31 (0.783)	2.47 (0.906)
	Median (range)	2.47 (0.86, 5.79)	2.11 (1.48, 4.26)	2.23 (0.58, 4.87)	2.32 (1.06, 5.12)
FVC (L)	Mean (SD)	3.45 (1.107)	3.48 (0.872)	3.31 (1.042)	3.40 (1.036)
	Median (range)	3.29 (1.21, 6.93)	3.32 (2.27, 5.34)	3.22 (1.20, 6.14)	3.23 (1.75, 5.70)
FEF_{25-75} (L)	Mean (SD)	2.19 (1.166)	1.85 (0.927)	1.91 (1.154)	2.08 (1.397)
	Median (range)	2.09 (0.55, 6.52)	1.73 (0.68, 4.34)	1.72 (0.46, 7.72)	1.74 (0.54, 7.68)
History of smoking	Prior smoker	23 (19)	7 (17)	24 (18)	8 (18)

Baseline Characteristics		Medium-Strength ICS		High-Strength ICS	
		FS MDPI 113 mcg/ 14 mcg b.i.d. (N = 120)	FS DPI 250 mcg/50 mcg b.i.d. (N = 41)	FS MDPI 232 mcg/ 14 mcg b.i.d. (N = 133)	FS DPI 500 mcg /50 mcg b.i.d. (N = 44)
	No tobacco use	97 (81)	34 (83)	109 (82)	36 (82)
Number of pack Years	Mean (SD)	2.8 (2.70)	4.4 (3.46)	4.4 (2.94)	3.8 (2.46)
	Median (range)	2.0 (0.0, 9.0)	4.0 (0.4, 9.7)	4.5 (0.2, 10.0)	4.3 (0, 7.5)
Duration of asthma	3 to < 6 months	0	0	1 (< 1)	0
	6 months to < 1 year	2 (2)	0	1 (< 1)	0
	1 to < 5 years	4 (3)	0	12 (9)	5 (11)
	5 to < 10 years	9 (8)	3 (7)	8 (6)	4 (9)
	10 to < 15 years	14 (12)	8 (20)	17 (13)	4 (9)
	15 years or longer	91 (76)	30 (73)	94 (71)	31 (70)
Concomitant asthma medication at screening, n (%)	Salbutamol	89 (74)	33 (80)	88 (66)	33 (75)
	Fluticasone propionate	3 (3)	5 (12)	5 (4)	1 (2)
	Beclomethasone dipropionate	1 (< 1)	0	3 (2)	1 (2)
	Budesonide	4 (3)	1 (2)	3 (2)	2 (5)
	Salbutamol sulphate	28 (23)	10 (24)	39 (29)	9 (20)
	Budesonide and formoterol fumarate	24 (20)	6 (15)	52 (39)	19 (43)
	Fluticasone propionate and salmeterol xinafoate (Seretide)	77 (64)	32 (78)	42 (32)	16 (36)
	Mometasone furoate and formoterol fumarate (Dulera)	19 (16)	3 (7)	35 (26)	9 (20)
	Mometasone furoate	2 (2)	0	0	0
	Ciclesonide	0	0	1 (< 1)	0
	Montelukast	0	2 (5)	2 (2)	0

b.i.d. = twice daily; BMI = body mass index; FEF_{25-75} = forced expiratory flow at 25% to 75%; FEV_1 = forced expiratory volume in one second; FS MDPI = fluticasone propionate / salmeterol xinafoate multidose dry powder inhaler; FS DPI = fluticasone propionate / salmeterol xinafoate dry powder inhaler; FVC = forced vital capacity; ICS = inhaled corticosteroid; n = number of patients with characteristic; N = total number of patients; SD = standard deviation.

Source: Clinical study report.[5]

Patient Disposition

Efficacy Trials (Study 301 and Study 30017)

In Study 301, a total of 1,363 patients with persistent asthma were screened for enrolment into this study (Table 15). Of the 1,363 patients screened, 787 patients at 129 investigational centres met entry criteria and were considered eligible for enrolment into this study. Of the screened patients, 576 patients were not enrolled. Of the 787 patients enrolled, 140 were not randomized — most commonly because of not meeting randomization criteria (70 patients).

In Study 30017, a total of 1,661 patients with persistent asthma were screened for enrolment into this study (Table 15). Of the 1,661 patients screened, 882 patients met entry criteria and were considered eligible for enrolment into the study of screened patients, and 779 patients were not enrolled. Of the 882 patients enrolled, 154 were not randomized — most commonly because of not meeting randomization criteria (76 patients).

Study completion was not consistent across treatment arms within each study. In Study 301, a lower proportion of patients randomized to the placebo arm completed the study (87%) than those in the FS MDPI 55 mcg/14 mcg twice daily (94%) and FS MDPI 113 mcg/14 mcg twice daily (98%) arms. Higher imbalances were observed in Study 30017, where 74% of patients in the placebo arm completed the study, compared with 92% in the FS MDPI 113 mcg/14 mcg arm, and 93% in the 232 mcg/14 mcg arm. The most commonly cited reasons for discontinuation among patients in both studies were disease progression, lack of efficacy, and AEs (including asthma-related AEs). Patient disposition for the Fp MDPI treatment arms in Study 301 and Study 30017 are presented in the clinical review report for Aermony RespiClick. In general, the patient disposition for the Fp MDPI arms were similar to the FS MDPI arms.

Table 15: Summary of Patient Disposition for Efficacy Trials (Study 301 and Study 30017)

Disposition	Study 301			Study 30017		
	Placebo	FS MDPI 55 mcg/ 14 mcg b.i.d.	FS MDPI 113 mcg/ 14 mcg b.i.d.	Placebo	FS MDPI 113 mcg/14 mcg b.i.d.	FS MDPI 232 mcg/ 14 mcg b.i.d.
Screened, N	1,363			1,661		
Randomized, N	130	129	129	145	145	146
ITT, N (%)	130 (100)	129 (100)	129 (100)	145 (100)	145 (100)	146 (100)
FAS, N (%)	129 (99)	128 (99)	126 (98)	143 (99)	141 (97)	145 (99)
Per-protocol, N (%)	128 (98)	127 (98)	126 (98)	140 (97)	143 (99)	144 (99)
Safety, N (%)	129 (99)	128 (99)	126 (98)	144 (99)	143 (99)	145 (99)
SSS — Randomized, N	60	56	61	61	58	68
SSS — ITT, N (%)	60 (100)	56 (100)	61 (100)	61 (100)	58 (100)	68 (100)
SSS — FAS, N (%)	60 (100)	56 (100)	61 (100)	61 (100)	58 (100)	68 (100)
SSS — completed study, N (%)	54 (90)	53 (95)	61 (100)	41 (67)	57 (98)	65 (96)
Total completed study, N (%)	113 (87)	121 (94)	126 (98)	107 (74)	136 (92)	136 (93)
Discontinued, N (%)	17 (13)	8 (6)	3 (2)	38 (26)	9 (6)	10 (7)
Disease progression, N (%)	2 (2)	0	0	18 (12)	1 (< 1)	2 (1)
Withdrawal by subject, N (%)	2 (2)	2 (2)	0	7 (5)	3 (2)	2 (1)
Lack of efficacy, N (%)	4 (3)	1 (< 1)	1 (< 1)	7 (5)	0	0
WDAEs, N (%)	6 (5)	3 (2)	0	2 (1)	2 (1)	2 (1)
Withdrawal due to SAEs, N (%)	2 (2)	0	1 (< 1)	1 (< 1)	2 (1)	2 (1)
Other, N (%)	1 (< 1)	1 (< 1)	3 (2)	2 (1)	0	1 (< 1)
Protocol violation, N (%)	1 (< 1)	0	0	1 (< 1)	1 (< 1)	1 (< 1)

Disposition	Study 301			Study 30017		
	Placebo	FS MDPI 55 mcg/ 14 mcg b.i.d.	FS MDPI 113 mcg/ 14 mcg b.i.d.	Placebo	FS MDPI 113 mcg/14 mcg b.i.d.	FS MDPI 232 mcg/ 14 mcg b.i.d.
Lost to follow-up, N (%)	1 (< 1)	1 (< 1)	0	1 (< 1)	1 (< 1)	1 (< 1)
Non-compliance, N (%)	0	0	0	0	0	0
Pregnancy, N (%)	0	0	0	0	0	1 (< 1)

b.i.d. = twice daily; FAS = full analysis set; FS MDPI = fluticasone propionate / salmeterol xinafoate multidose dry powder inhaler; ITT = intention-to-treat; N = total number of patients; SAE = serious adverse event; SSS = serial spirometry set; WDAE = withdrawal due to adverse event.

Source: Clinical study reports.[3,4]

Safety Trial (Study 305)

Table 16 provides a summary of the patient disposition from the ICS/LABA cohorts of the safety study. For both the medium-strength and high-strength comparisons, the proportion of patients who discontinued the studies was similar between the FS DPI arms and the FS MDPI arms (12% versus 8% and 13% versus 14%, respectively). Withdrawal by patient was the most commonly cited reason for all arms (3% to 7%). Patient disposition for the Fp MDPI treatment arms in Study 305 are presented in the clinical review report for Aermony RespiClick. In general, patient disposition for the Fp MDPI arms was similar to the FS MDPI arms.

Table 16: Patient Disposition in Safety Trial (Study 305)

Disposition, n (%)	Medium-Strength		High-Strength	
	FS MDPI 113 mcg/14 mcg b.i.d. (N = 120)	FS DPI 250 mcg/50 mcg b.i.d. (N = 41)	FS MDPI 232 mcg/14 mcg b.i.d. (N = 133)	FS DPI 500 mcg/50 mcg b.i.d. (N = 44)
Randomized	120 (100)	41 (100)	133 (100)	44 (100)
Not treated	0	0	0	0
ITT population	120 (100)	41 (100)	133 (100)	44 (100)
Safety population	120 (100)	41 (100)	133 (100)	44 (100)
Full analysis set	119 (> 99)	40 (98)	130 (98)	44 (100)
Completed	110 (92)	36 (88)	116 (87)	38 (87)
Discontinued	10 (8)	5 (12)	17 (13)	6 (14)
Death	0	0	0	0
Adverse event	3 (3)	2 (5)	0	1 (2)
Withdrawal by patient	4 (3)	2 (5)	9 (7)	2 (5)
Nonadherence	0	0	0	1 (2)
Protocol violation	0	0	1 (< 1)	0
Disease progression	0	0	2 (2)	0
Pregnancy	0	0	0	0
Lost to follow-Up	2 (2)	1 (2)	2 (2)	2 (5)
Lack of efficacy	1 (< 1)	0	1 (< 1)	0
Other	0	0	2 (2)	0

b.i.d. = twice daily; FS MDPI = fluticasone propionate / salmeterol xinafoate multidose dry powder inhaler; FS DPI = fluticasone propionate/ salmeterol xinafoate dry powder inhaler; ITT = intention-to-treat; n = number of events; N = total number of patients.

Source: Clinical study report.[5]

Efficacy

Primary Efficacy End Point

Trough FEV_1

In Study 301, results for the change in baseline in trough FEV_1 at week 12 in the FS MDPI arms were statistically significantly superior to those in the placebo arm in the full analysis set ($P < 0.0001$ for each; see Table 8). Comparisons of combination therapy with monotherapy in the full analysis set were not controlled for multiplicity, but indicated improvement for FS MDPI 55 mcg/14 mcg compared with FP MDPI 55 mcg ($P = 0.0022$) and with FS MDPI 113 mcg ($P = 0.0166$), and of FS MDPI 113 mcg/14 mcg compared with FP MDPI 113 mcg ($P = 0.0202$).

In Study 30017, results for change from baseline in trough FEV_1 at week 12 in the FS MDPI arms were statistically significantly superior to those in the placebo arm in the full analysis set ($P <0.0001$ for each). Comparisons of combination therapy with monotherapy in the full analysis set were not controlled for multiplicity, but indicated improvement for FS MDPI 113 mcg/14 mcg compared with FP MDPI 113 mcg ($P = 0.0005$) and with FP MDPI 232 mcg ($P = 0.0356$), and of FS MDPI 232 mcg/14 mcg compared with FP MDPI 232 mcg ($P = 0.0309$).

Results for change from baseline in trough FEV_1 at week 12 in the FP MDPI arms were statistically significantly superior to those in the placebo arm in the full analysis set ($P = 0.0047$ for FP MDPI 113 mcg and $P < 0.0001$ for FP MDPI 232 mcg).

Table 17: Change From Baseline in Trough FEV_1 (L) at Week 12 for Efficacy Trials

Comparison	Study 301			Study 30017		
	Placebo	FS MDPI 55 mcg/ 14 mcg b.i.d.	FS MDPI 113 mcg/ 14 mcg b.i.d.	Placebo	FS MDPI 113 mcg/ 14 mcg b.i.d.	FS MDPI 232 mcg/ 14 mcg b.i.d.
N	129	128	126	143	140	145
Baseline	2.188	2.302	2.162	2.132	2.154	2.083
Change from baseline (LS mean, 95% CI)	0.053 (−0.015, 0.122)	0.319 (0.250, 0.388)	0.315 (0.246, 0.385)	0.000 (−0.065, 0.057)	0.271 (0.210, 0.332)	0.272 (0.212, 0.333)
Comparison with placebo (95% CI)	–	0.266 (0.172, 0.360)	0.262 (0.168, 0.356)	–	0.274 (0.189, 0.360)	0.276 (0.191, 0.361)
Comparison with Fp MPDI 55 mcg b.i.d. (95% CI)	–	0.147 (0.053, 0.242)	–	–	–	–
Comparison with Fp MPDI 113 mcg b.i.d. (95% CI)	–	0.115 (0.021, 0.210)	0.111 (0.017, 0.206)	–	0.152 (0.066, 0.237)	–
Comparison with Fp MPDI 232 mcg b.i.d. (95% CI)	–	–	–	–	0.092 (0.006, 0.177)	0.093 (0.009, 0.178)

b.i.d. = twice daily; CI = confidence interval; FEV_1 = forced expiratory volume in one second; Fp MDPI = fluticasone propionate multidose dry powder inhaler; FS MDPI = fluticasone propionate/ salmeterol xinafoate multidose dry powder inhaler; LS = least squares; N = total number of patients.

Source: Clinical study reports.[3,4]

In the safety study, similar results were observed for the pooled analysis of the FS MDPI and FS DPI arms for the efficacy assessment in this study. The change from baseline in trough FEV_1 over the 26-week period was 0.108 L (95% CI, 0.074, 0.142) in the FS MDPI

arm and 0.079 L (95% CI, 0.022, 0.136) in the FS DPI arm. This yielded a least squares mean change from baseline difference in trough FEV_1 of FS MDPI from the FS DPI arms of 0.029 L (95% CI, -0.036, 0.095, *P* = 0.3821). Therefore, the treatment effect and lower limit of the 95% CI exceeded the −0.125 L noninferiority margin for FEV_1. The results in least squares mean change from baseline in trough FEV_1 over the 26-week period are also shown in Table 18 for the two individual dosage arms, which appear to have been performed ad hoc. The treatment differences were found to be 0.000 L between the FS MDPI 113 mcg/14 mcg and FS DPI 250 mcg/50 mcg arms (95% CI, −0.095, 0.095, *P* = 0.9966) and 0.059 L between the FS MDPI 232 mcg/14 mcg and FS DPI 500 mcg/50 mcg arms (95% CI, −0.032, 0.150, *P* = 0.2056). Both arms had the lower limit of the 95% CI exceeding the −0.125 L noninferiority margin for FEV_1.

Table 18: Analysis of Change From Baseline in Trough FEV_1 (L) Over 26-Week Treatment Period for Study 305

Variable	Medium-Dose Strength		High-Dose Strength		High-/Medium-Strength Combined	
	FS MDPI 113 mcg/14 mcg b.i.d. (N = 119)	FS DPI 250 mcg/ 50 mcg b.i.d. (N = 40)	FS MDPI 232 mcg/ 14 mcg b.i.d. (N = 130)	FS DPI 500 mcg/ 50 mcg b.i.d. (N = 44)	FS MDPI b.i.d. (N = 249)	FS DPI b.i.d. (N = 84)
LS Mean (SE)	0.116 (0.0251)	0.117 (0.0419)	0.100 (0.0235)	0.041 (0.0399)	0.108 (0.0173)	0.079 (0.0290)
95% CI	(0.067, 0.166)	(0.034, 0.199)	(0.054, 0.146)	(−0.037, 0.119)	(0.074, 0.142)	(0.022, 0.136)
Comparison With FS DPI						
Difference of LS mean (SE)	0.000 (0.0485)		0.059 (0.0464)		0.029 (0.0335)	
95% CI	(−0.095, 0.095)		(−0.032, 0.150)		(−0.036, 0.095)	
P value	0.9966		0.2056		0.3821	

b.i.d. = twice daily; CI = confidence interval; FEV_1 = forced expiratory volume in one second; FS DPI = fluticasone propionate / salmeterol xinafoate dry powder inhaler; FS MDPI = fluticasone propionate / salmeterol xinafoate multidose dry powder inhaler; LS = least squares; N = total number of patients; *P* = probability; SE = standard error.

Source: Clinical study report.[5]

The tipping point analysis results for both placebo-controlled studies, Study 301 and Study 30017, are presented in Table 19. In terms of change from baseline trough FEV_1, for the comparison of FS MDPI 232 mcg/14 mcg over placebo in Study 30017, the estimated treatment effect at week 12 was 0.276 L from the m-baseline-observation carried forward ANCOVA model, and the estimated treatment effect over the 12-week treatment period from the MMRM analysis based on observed data were 0.244 L. For most of the comparisons, an assumed shift in the missing data assumptions on the experimental treatment arm of roughly nine-fold (−2.60 versus 0.266 in FS MDPI 55 mcg/14 mcg versus placebo in Study 301) to 20-fold (−5.48 versus 0.262 in FS 113 mcg/14 mcg versus placebo in Study 301) times the size of the treatment effect would be needed to tip the positive decision on treatment efficacy. In addition, the range of tipping points from −2.60 L to −5.48 L includes values that are not possible. With these considerations, 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 19: 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 12-Week Treatment Period (95% CI, *P* Value)	Tipping Point
Study 301			
FS MDPI 55 mcg/14 mcg b.i.d. vs. Placebo	0.266 (0.172, 0.360) *P* < 0.001	0.256 (0.177, 0.335) *P* < 0.001	−2.60
FS MDPI 232 mcg/14 mcg b.i.d. vs. Placebo	0.262 (0.168, 0.356) *P* < 0.001	0.243 (0.164, 0.322) *P* < 0.001	−5.48
Study 30017			
FS MDPI 113 mcg/14 mcg b.i.d. vs. Placebo	0.274 (0.189, 0.360) *P* < 0.001	0.226 (0.158, 0.295) *P* < 0.001	−3.63
FS MDPI 232 mcg/14 mcg b.i.d. vs. Placebo	0.276 (0.191, 0.361) *P* < 0.001	0.244 (0.176, 0.312) *P* < 0.001	−3.66

ANCOVA = analysis of covariance; b.i.d. = twice daily; CI = confidence interval; FEV_1 = forced expiratory volume in one second; FS MDPI = fluticasone propionate / salmeterol xinafoate multidose dry powder inhaler; ICS = inhaled corticosteroid; ICS/LABA = inhaled corticosteroid and long-acting beta2 agonist; MMRM = mixed model repeated measures; *P* = probability; vs. = versus.

[a] Treatment comparisons and analysis are 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 baseline-observation carried forward.

Source: Clinical study reports.[3,4]

FEV_1 $AUEC_{0\text{-}12\ h}$

In Study 301, results for the standardized baseline-adjusted FEV_1 $AUEC_{0\text{-}12\ h}$ based on serial spirometry for combination therapy compared with monotherapy in the full analysis set indicated that FS MDPI 113 mcg/14 mcg was statistically significantly superior to Fp MDPI 113 mcg (*P* = 0.0076) and that FS MDPI 55 mcg/14 mcg was statistically significantly superior to FP MDPI 55 mcg (*P* = 0.0322) (Table 10). There was also improvement for FS MDPI 55/14 mcg compared with Fp MDPI 113 mcg (unadjusted *P* = 0.0151).

In Study 30017, results for the standardized baseline-adjusted FEV_1 $AUEC_{0\text{-}12\ h}$ based on serial spirometry for combination therapy compared with monotherapy in the full analysis set indicated that FS MDPI 232 mcg/14 mcg was statistically significantly superior to Fp MDPI 232 mcg (*P* = 0.0009) and that FS MDPI 113 mcg/14 mcg was statistically significantly superior to FP MDPI 113 mcg (*P* = 0.0010). There was also improvement for FS MDPI 113 mcg/14 mcg compared with FP MDPI 232 mcg (unadjusted *P* = 0.0017).

Results for the standardized baseline-adjusted FEV_1 $AUEC_{0\text{-}12\ h}$ based on serial spirometry in the FS MDPI arms were statistically significantly superior to those in the placebo arm in the full analysis set (*P* < 0.0001 for each).

Table 20: Standardized Baseline-Adjusted FEV_1 $AUC_{0\text{-}12\ h}$ (L) at Week 12 for Placebo-Controlled Studies in Serial Spirometry Subset

Comparison	Study 301			Study 30017		
	Placebo	FS MDPI 55 mcg/ 14 mcg b.i.d.	FS MDPI 113 mcg/ 14 mcg b.i.d.	Placebo	FS MDPI 113 mcg/ 14 mcg b.i.d.	FS MDPI 232 mcg/ 14 mcg b.i.d.
N	60	56	61	61	58	68
Baseline LS mean (95% CI)	0.074 (−0.022, 0.170)	0.399 (0.305, 0.493)	0.408 (0.317, 0.500)	0.121 (28, 214)	0.442 (345, 540)	0.446 (355, 538)
Comparison with placebo (95% CI)	–	0.325 (0.203, 0.447)	0.335 (0.216, 0.453)	–	0.322 (0.212, 0.432)	0.326 (221, 431)
Comparison with Fp MDPI 55 mcg b.i.d. (95% CI)	–	0.131 (0.011, 0.250)	–	–	–	–
Comparison with Fp MDPI 113 mcg b.i.d. (95% CI)	–	0.145 (0.028, 0.261)	0.154 (0.041, 0.267)	–	0.182 (0.074, 0.291)	–
Comparison with Fp MDPI 232 mcg b.i.d. (95% CI)	–	–	–	–	0.175 (0.066, 0.284)	0.179 (0.074, 0.285)

b.i.d. = twice daily; CI = confidence interval; FEV_1 $AUEC_{0\text{-}12\ h}$ = standardized baseline-adjusted area under the effect curve for forced expiratory volume in one second from zero to 12 hours post dose; Fp MDPI = fluticasone propionate multidose dry powder inhaler; FS MDPI= fluticasone propionate / salmeterol xinafoate multidose dry powder inhaler; LS = least squares; N = total number of patients.

Source: Clinical study reports.[3,4]

Secondary Efficacy End Points

Study 301

Change from baseline in the weekly average of the daily trough morning PEF:

- Results for the change from baseline in the weekly average of the daily trough morning PEF in the FS MDPI arms were statistically significantly superior to those in the placebo group ($P < 0.0001$ for each).
- Comparisons of combination therapy with monotherapy indicated that FS MDPI 113 mcg/14 mcg was statistically significantly superior to Fp MDPI 113 mcg ($P = 0.0233$) and that FS MDPI 55 mcg/14 mcg was statistically significantly superior to Fp MDPI 55 mcg ($P = 0.0011$) and to Fp MDPI 113 mcg ($P = 0.0175$).

Change from baseline in the weekly average of the total daily asthma symptoms score over weeks 1 to 12:

- Results for change from baseline in the weekly average of the total daily asthma symptoms score over weeks 1 to 12 in the FS MDPI arms were statistically significantly superior to those in the placebo group ($P < 0.0001$ for each).
- Results for combination therapy were better than those for monotherapy.

Change from baseline in the weekly average of total daily use of albuterol / salbutamol inhalation aerosol over weeks 1 to 12:

- Results for the change from baseline in the weekly average of the total daily (24-hour) use of albuterol / salbutamol inhalation aerosol (number of inhalations) over weeks 1 to 12 in the FS MDPI arms were statistically significantly superior to those in the placebo arm ($P < 0.0001$ for each).
- Results for combination therapy were better than those for monotherapy.

Study 30017

Change from baseline in the weekly average of the daily trough morning PEF:

- Results for change from baseline in the weekly average of the daily trough morning PEF in the FS MDPI arms were statistically significantly superior to those in the placebo arm ($P < 0.0001$ for each).
- Comparisons of combination therapy with monotherapy indicated that FS MDPI 232 mcg/14 mcg was statistically significantly superior to Fp MDPI 232 mcg ($P = 0.0002$) and that FS MDPI 113 mcg/14 mcg was statistically significantly superior to Fp MDPI 113 mcg ($P = 0.0002$) and to Fp MDPI 232 mcg ($P = 0.0010$).

Change from baseline in the weekly average of the total daily asthma symptoms score over weeks 1 to 12:

- Results for change from baseline in the weekly average of the total daily asthma symptoms score over weeks 1 to 12 in the FS MDPI arms were statistically significantly superior to those in the placebo arm ($P < 0.0001$ for each).
- Comparisons of combination therapy with monotherapy indicated that FS MDPI 232 mcg/14 mcg was statistically significantly superior to Fp MDPI 232 mcg ($P = 0.0014$), that FS MDPI 113 mcg/14 mcg was numerically superior to Fp MDPI 113 mcg, and that there was a trend in favour of FS MDPI 113 mcg/14 mcg relative to Fp MDPI 232 mcg ($P = 0.0094$).

Change from baseline in the weekly average of total daily use of albuterol / salbutamol inhalation aerosol over weeks 1 to 12:

- Results for the change from baseline in the weekly average of the total daily (24-hour) use of albuterol / salbutamol inhalation aerosol (number of inhalations) over weeks 1 to 12 in the FS MDPI arms were statistically significantly superior to those in the placebo arm ($P < 0 .0001$ for each).
- Comparisons of combination therapy with monotherapy indicated that FS MDPI 232 mcg/14 mcg was statistically significantly superior to Fp MDPI 232 mcg ($P =0.0160$), and that there were trends in favour of FS MDPI 113/14 mcg compared with Fp MDPI 113 mcg ($P = 0.0124$) and Fp MDPI 232 mcg ($P = 0.0588$).

Change from Baseline in the AQLQ(S) Score at Week 12 or at end point:

- Change from baseline, particularly at end point, showed differentiation between the active treatment arms and placebo, and between FS MDPI and Fp MDPI.
- Results for change from baseline in the AQLQ(S) score in the FS MDPI arms were statistically significantly superior to those in the placebo arm at end point ($P = 0.0017$ for FS MDPI 55 mcg/14 mcg and $P < 0.0001$ for FS MDPI 113 mcg/14 mcg). Week 12 results were similar.
- Results for combination therapy were better than those for monotherapy at end point. Week 12 results were similar.
- These results suggest some dose-dependent differentiation between the FS MDPI 55 mcg/14 mcg and FS MDPI 113 mcg/14 mcg arms at end point and at week 12.

In completing the review report template, the manufacturer summarized data related to asthma exacerbations in section 2.3.

Table 21: Secondary End Points for Efficacy Studies

Comparison	Study 301			Study 30017		
	Placebo	FS MDPI 55 mcg/ 14 mcg b.i.d.	FS MDPI 113 mcg/ 14 mcg b.i.d.	Placebo	FS MDPI 113 mcg/ 14 mcg b.i.d.	FS MDPI 232 mcg/ 14 mcg b.i.d.
Change From Baseline in the Weekly Average of the Total Daily Trough Morning PEF (mL/minute.) Over Weeks 1 to 12						
N	128	128	125	142	141	145
Baseline	358	360	352	351	357	343
Change from baseline (LS mean [SE], 95% CI)	4 (3) (−3, 10)	25 (3) (19, 31)	24 (3) (18, 31)	−11 (3) (−16, −6)	19 (2) (14, 23)	20 (3) (16, 25)
Comparison with placebo (95% CI)	–	21 (13, 30)	21 (12, 29)	–	30 (23, 36)	31 (25, 38)
Comparison with Fp MDPI 55 mcg b.i.d. (95% CI)	–	14 (6, 23)	–	–	–	–
Comparison with Fp MDPI 113 mcg b.i.d. (95% CI)	–	11 (2, 19)	10 (1, 18)	–	13 (6, 20)	–
Comparison with Fp MDPI 232 mcg b.i.d. (95% CI)	–	–	–	–	11 (5, 18)	13 (6, 19)
Change From Baseline in the Weekly Average of the Total Daily Asthma Symptoms Score (Range 0-4.5) Over Weeks 1 to 12						
N	128	128	125	142	141	145
Baseline	0.80	0.78	0.78	0.88	0.95	0.94
Change from baseline (LS mean [SE], 95% CI)	−0.14 (0.04) (−0.20, −0.07)	−0.33 (0.03) (−0.39, −0.27)	−0.36 (0.03) (−0.43, −0.30)	−0.09 (0.03) (−0.15, −0.02)	−0.36 (0.03) (−0.43, −0.30)	−0.39 (0.03) (−0.46, −0.33)
Comparison with placebo (95% CI)	–	-0.19 (-0.28, -0.11)	−0.23 (−0.32, −0.14)	–	−0.28 (−0.37, −0.18)	−0.30 (−0.40, −0.21)
Comparison with Fp MDPI 55 mcg b.i.d. (95% CI)	–	-0.05 (-0.14, 0.04)	–	–	–	–
Comparison with Fp MDPI 113 mcg b.i.d. (95% CI)	–	0.03 (-0.11, 0.06)	−0.06 (−0.15, 0.02)	–	−0.08 (−0.17, 0.01)	–
Comparison with Fp MDPI 232 mcg b.i.d. (95% CI)	–	–	–	–	-0.12 (−0.21, −0.03)	−0.15 (−0.24, −0.06)
Change From Baseline in Weekly Average of the Total Daily Use of Salbutamol/Albuterol						
N	129	128	126	143	141	145
Baseline (number of inhalations)	1.4	1.2	1.1	1.7	2.0	1.9
Change from baseline (LS Mean [SE], 95% CI)	0	−0.71 (0.09) (−0.89, −0.52)	−0.68 (0.09) (−0.86, −0.49)	0.17 (0.11) (−0.05, 0.39)	−0.82 (0.11) (−1.03, −0.61)	−0.90 (0.11) (−1.11, −0.69)
Comparison with placebo (95% CI)	–	−0.70 (−0.96, −0.45)	−0.68 (−0.93, −0.42)	–	−0.99 (−1.29, −0.69)	−1.07 (−1.37, −0.77)
Comparison with Fp MDPI 55 mcg b.i.d. (95% CI)	–	−0.24 (−0.50, 0.01)	–	–	–	–
Comparison with Fp MDPI 113 mcg b.i.d. (95% CI)	–	-0.24 (−0.49, 0.01)	−0.21 (−0.47, 0.04)	–	−0.38 (−0.68, −0.08)	–
Comparison with Fp MDPI 232 mcg b.i.d. (95% CI)	–	–	–	–	−0.29 (−0.58, 0.01)	−0.36 (−0.66, −0.07)

Comparison	Study 301			Study 30017		
	Placebo	FS MDPI 55 mcg/ 14 mcg b.i.d.	FS MDPI 113 mcg/ 14 mcg b.i.d.	Placebo	FS MDPI 113 mcg/ 14 mcg b.i.d.	FS MDPI 232 mcg/ 14 mcg b.i.d.
Change From Baseline in Weekly Average of the AQLQ at Week 12 or End Point						
N	110	108	109	129	135	131
Baseline AQLQ weekly score	4.9	5.1	5.0	4.9	4.9	5.0
Change from baseline (LS mean [SE]) (95% CI)	0.21 (0.08) (0.06, 0.35)	0.54 (0.08) (0.39, 0.69)	0.82 (0.08) (0.67, 0.97)	−0.09 (0.07) (−0.24, 0.06)	0.59 (0.07) (0.45, 0.74)	0.53 (0.07) (0.39, 0.68)
Comparison with Placebo (95% CI)	–	0.33 (0.13, 0.54)	0.61 (0.4, 0.81)	–	0.68 (0.48, 0.89)	0.62 (0.41, 0.83)
Comparison with Fp MDPI 55 mcg b.i.d. (95% CI)	–	−0.02 (−0.23, 0.18)	–	–	–	–
Comparison with Fp MDPI 113 mcg b.i.d. (95% CI)	–	−0.07 (−0.28, 0.14)	0.21 (0.00, 0.42)	–	0.25 (0.05, 0.46)	–
Comparison with Fp MDPI 232 mcg b.i.d. (95% CI)	–	–	–	–	0.21 (0.01, 0.41)	0.15 (−0.05, 0.35)

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; FS MDPI = fluticasone propionate / salmeterol xinafoate multidose dry powder inhaler; LS = least squares; min. = minimum; N = total number of patients; PEF = peak expiratory flow; SE = standard error.

Source: Clinical study reports.[3,4]

2.2 Critical Appraisal of Pivotal Clinical Studies

2.2.1 Internal Validity

- In Study 301, baseline patient characteristics appeared to have a few differences between treatment arms. For example, this trial had a slightly lower median FEV_1 in the placebo arm (2.095 L) compared with those in the FS MDPI 55 mcg/14 mcg (2.238 L) and 113 mcg/14 mcg (2.133 L) arms, as well as a lower mean per cent of predicted FEV_1 in the placebo arm (66.96%) compared with the FS MDPI 55 mcg/14 mcg (69.71%) and FS MDPI 113 mcg/14 mcg (67.11%) arms. In Study 30017, a higher proportion of patients had previously taken montelukast in the FS MDPI 113 mcg/14 mcg arm (5%) compared with those in the placebo arm (2%) and those in the FS MDPI 232 mcg/14 mcg arm (2%). Montelukast is a leukotriene receptor antagonist; therefore, its use was prohibited seven days prior to screening. Montelukast is considered a third-line agent for use in the treatment of asthma, and the fact that this medication was discontinued prior to screening can lead to an unpredictable effect on control of asthma in these patients. None of the imbalances are expected to have had a notable impact on outcomes in the studies.
- In Study 305, a few imbalances were noted between treatment arms. The majority of patients in all treatment arms were between 18 and 64 years of age, with the FS DPI 500 mcg/50 mcg arm containing the largest proportion of these patients (93%) relative to the other treatment arms (76% to 80%). Within the medium-strength ICS/LABA cohort, the 113 mcg/14 mcg FS MDPI arm had a higher mean FEV_1 at baseline compared with those in the FS DPI 250 mcg/50 mcg arm (2.54 L versus 2.44 L, respectively). In addition, 5% of patients in the FS MDPI 113 mcg/14 mcg category had asthma for less than five years compared with none in the FS DPI 250 mcg/50 mcg arm. Within the high-strength ICS/LABA cohort, the 232 mcg/14 mcg FS MDPI arm had a slightly lower mean FEV_1 at baseline compared with those in the FS DPI 500 mcg/50 mcg arm (2.31 L versus 2.47 L, respectively).

- Within the medium-strength ICS/LABA cohort of Study 305, none of the patients in the FS MDPI 113 mcg/14 mcg arm were concomitantly using montelukast, compared with 5% of those in the FS DPI 250 mcg/50 mcg arm. Within the high-strength ICS/LABA cohort of this study, 2% of patients in the FS MDPI 232 mcg/14 mcg arm were taking montelukast, whereas none of the patients in the FS DPI 500 mcg/50 mcg arm were. In this study, montelukast was not listed as a prohibited medication; however, it is possible that patients taking this medication have more advanced asthma, potentially leading to an imbalance in treatment groups.
- The only study with an active comparator was an open-label study designed to be primarily a safety study. The comparison was between FS MDPI and another fluticasone propionate/ salmeterol xinafoate preparation, FS DPI, and the efficacy outcome within this study was defined as change from baseline in trough FEV_1 at week 26. This outcome was defined a priori for which it had 90% power of determining noninferiority between the pooled medium- and high-dose arms of FS MDPI and the pooled medium- and high-dose arms of FS DPI. 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)[36] and the minimally perceivable improvement from baseline in trough FEV_1 reported in the literature (0.23 L),[37] which may be reasonable in the context of what appears to be a clinically derived noninferiority margin as per FDA guidance.[38] Results were presented for pooled doses with respect to this outcome, as well as for the separate arms comparing FS MDPI 113 mcg/14 mcg with FS DPI 250 mcg/50 mcg, and FS MDPI 232 mcg/14 mcg with FS DPI 500 mcg/50 mcg. These noninferiority analyses comparing the separate dosage arms of FS MDPI with FS DPI appear to have been performed ad hoc and do not seem to be adjusted for multiplicity, which would limit its interpretation.
- During the run-in period of the safety study, Study 305, patients were instructed to continue using their current ICS and/or other controller therapies, and to discontinue their current short-acting beta2 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 FS DPI or FS MDPI. The half-life of both of these treatments is about eight hours but due to the lack of an adequate washout period, it is difficult to rule out that any clinical changes seen in this study could have been due to the patient initially being stable on their current ICS/LABA treatment.
- There was a higher rate of patient discontinuation in the placebo arms compared with the FS MDPI arms in the 12-week placebo-controlled trials, Study 301 and Study 30017. In the adjusted ANCOVA model used in the primary analysis, missing data caused by early dropout was imputed using the baseline-observation carried forward 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 assigned a poor score. To impute missing FEV_1 values for these patients who discontinued treatment before week 12, a tipping point sensitivity analysis was 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 arm due to worsening asthma may not have been adequately captured, thereby potentially biasing results in favour of fluticasone propionate / salmeterol xinafoate. Of note, the FDA

statistical reviewer conducted several sensitivity analyses and concluded that these analyses agreed with the main analysis.[34]

- Study 301 and Study 30017 were designed with the primary objective of establishing superiority of fluticasone propionate / salmeterol xinafoate over Fp, followed by superiority of fluticasone propionate / salmeterol xinafoate 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 being 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,[34] the manufacturer's hierarchy approach for the analyses of secondary end points in Study 301 and Study 30017 controlled the type I error for comparisons at a particular study drug and strength, as well as comparisons over study drugs and 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; but their approach was not modified. Therefore, results for the secondary end points of these studies should be interpreted with this in mind.
- All efficacy analyses were based on the full analysis set, which included all patients who received any dosage of study medication and had a non-missing baseline and at least one non-missing post-baseline trough FEV_1 measurement. For all included studies, supportive primary analyses were also conducted for the primary outcomes with the ITT population. Results of the supportive primary analyses were similar to those based on the full analysis set.
- Inclusion criteria for the efficacy studies, Study 301 and Study 30017, stipulated that patients were required to meet specific qualifying dosages of equivalent ICS inhalers to be considered for inclusion in respective studies. The qualifying dosages provided (Table 6) were ranges based on previous ICS or ICS/LABA therapy. There was no specification provided as to what qualified as low, medium, or high ICS dosage ranges. Therefore, it was unclear how the decision was made to place patients into respective FS MDPI 55 mcg/14 mcg, 113 mcg/14 mcg, and 232 mcg/14 mcg arms after inclusion criteria was met. The possibility of patients enrolled in Study 301 being mismatched to a low-dose (55 mcg/14 mcg) or medium-dose (113 mcg/14 mcg) FS MDPI arm, or those enrolled in Study 30017 being mismatched to a medium-dose (113 mcg/14 mcg) or high-dose (232 mcg/14 mcg) FS MDPI arm based on their previous dosage, cannot be ruled out.
- The efficacy studies were both double-blinded. However, placebo arms showed the highest rates of premature discontinuation, withdrawal due to lack of efficacy, and short-duration exposure, suggesting that blinding may have been compromised in these arms. The majority of secondary outcomes in these studies were patient-reported; therefore, outcome assessment might be biased in favour of the active treatments for these outcomes. In addition, a patient's knowledge of his or her treatment may have affected efforts placed on the spirometer testing, which has the potential to raise uncertainty around the FEV_1 comparisons versus placebo.
- Prior to screening for the efficacy trials, patients were to discontinue their current asthma regimen, including ICS or ICS/LABA treatment. During the run-in period, patients were instructed to take one inhalation of open-label beclomethasone dipropionate 40 mcg HFA MDP 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 treatments. The clinical expert involved in this review expressed concern that these patients were suboptimally treated

during these run-in periods, 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 FS MDPI in these studies.

- Many of the secondary efficacy outcomes included in all studies, such as asthma symptoms scores, AQLQ(S), asthma control tests, and use of rescue medication, were diary entries; therefore, the subjectivity of these values may have been impacted by the fact that many patients in the placebo arm could have been unblinded due to poor control, potentially increasing risk of bias in favour of treatment.

2.2.2 External Validity

- FS MDPI delivers a lower nominal dose of fluticasone propionate/ salmeterol xinafoate than Advair Diskus (FS DPI), and pharmacokinetic studies suggested that systemic exposure of FS MDPI is lower than or similar to Advair Diskus. However, there remains uncertainty as to whether FS MDPI will elicit a similar level of efficacy with existing fluticasone propionate / salmeterol xinafoate preparations, due to the fact that both efficacy studies were placebo-controlled and only one efficacy outcome in the safety trial was powered to detect noninferiority (not equivalence) in pooled dosage arms. Head-to-head comparisons were conducted in the phase II dose-ranging study, Study FSS-201 (Appendix 4), which found no statistically significant difference between FS MDPI 113mcg/14 mcg and Advair Diskus 100mcg/50 mcg for the change from baseline in standardized baseline-adjusted FEV_1 AUC over 12 hours post-dose, though limitations associated with these studies mean there is uncertainty regarding the comparative efficacy. Furthermore, the safety outcomes in the safety trial have not presented any indication of discernable improvement compared with FS DPI; therefore, it is unknown whether any long-term benefits can be seen from this reported reduced systemic exposure. The maximum daily dose in the product monograph for FS MDPI is 464 mcg/30 mcg (one inhalation of 232 mcg/14 mcg twice daily).[28] This created concern that if a patient is not optimally treated on this dose, another preparation would need to be used, or that prescribers would be forced to use this product off-label. [redacted] As a result, equivalence with a comparator was not a consideration for Health Canada approval of FS 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). The clinical expert consulted for this review also questioned whether the marketed dosage for FS MDPI would cause confusion among Canadian prescribers who are familiar with dosages on current Advair products.
- The patients enrolled in Study 301 and Study 30017 were predominantly female (58%), Caucasian (80%), had never smoked (86%), and were 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 compliance. Also, the overwhelming majority of patients in this study being Caucasian may limit the generalizability of these results to patients of other races.

- The number of patients screened in Study 301 and Study 30017, and subsequently not enrolled, was high in both studies. In Study 301, 1,363 patients were screened, and 576 were not enrolled; in Study 30017, 1,661 patients were screened, 779 of whom were not enrolled. In most of these cases (80% in Study 301, 67% in Study 30017), this was due to the fact that inclusion criteria were not met, which significantly limited the generalizability of this data.
- All identified trials recruited patients ≥ 12 years of age. In 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 impacted 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 chronically for a condition such as asthma.
- Baseline asthma severity was evaluated by FEV_1; and the pre-bronchodilator percentage predicted FEV_1 for the placebo-controlled trials ranged from 64.7% to 69.1%. These values indicate that the included patients appeared to have been suboptimally treated for their asthma prior to enrolment in the studies. Therefore, results might be biased in favour of the active treatment arms because patients in these arms would have their treatment dosage improved while placebo patients would have their suboptimal active ICS or ICS/LABA switched to placebo.
- The clinical expert consulted in 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, 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.

2.3 Summary of Safety

Three pivotal trials were performed: two trials comparing FS MDPI with placebo to evaluate efficacy (Study 301 and Study 30017), with safety as a patient-reported secondary outcome, and one open-label long-term safety trial comparing FS MDPI and FS DPI (Study 305). Study 305 evaluated safety, with the primary outcome being measure of incidence and type of AEs for two strengths of both FS MDPI and FS DPI. The incidence of adverse reactions with FS MDPI was also reported in Study 301 and Study 30017 as a secondary patient-reported outcome.

2.3.1 Study 301 and Study 30017

In Study 301, safety was assessed through physical examinations and AEs. Safety data indicated that treatment with FS MDPI for up to 12 weeks was safe, with incidence rates of AEs similar across treatment arms. Additionally, the types of events were consistent for the drug class and patient population, with AEs including nasopharyngitis, cough, and upper respiratory infection. Oral candidiasis was more common in the active treatment arm compared with placebo, which was expected. Asthma exacerbation was also recorded (seven patients in placebo [5%]; six patients in active treatment [1.2%]). Four patients (3%) in the placebo group who experienced at least one asthma exacerbation were either

hospitalized or discontinued, compared with one patient (< 1%) who was actively treated with FS MDPI.

Safety was assessed in the same manner for Study 30017 as in Study 301. Incidence rates were also similar in this study. One patient treated with FS MDPI 113 mcg/14 mcg died due to fulminant liver failure. The event occurred in a 44-year-old black female after receiving FS MDPI 113 mcg/14 mcg (one inhalation twice daily) for 37 days and starting a new herbal supplement (moringa oleifera) on day 22. Her liver function tests continued to be elevated and she died on day 72. The number of patients with at least one exacerbation was higher in the placebo arm (23 patients [16%]) compared with those actively being treated with FS MDPI (nine patients [2%]); however, none required hospitalization. For 26 patients (19 patients in placebo [13%] and seven patients in active treatment [1.2%]), exacerbation led to discontinuation of the study drug treatment.

The incidence of adverse reactions associated with FS MDPI in Table 31 in Appendix 3 is based upon Study 301 and Study 30017. A total of 1,364 adolescent and adult patients (798 females and 566 males) previously treated with ICSs were treated twice daily with Fp MDPI 55 mcg, 113 mcg, or 232 mcg; or FS MDPI 55 mcg/14 mcg, 113 mcg/14 mcg, or 232 mcg/14 mcg; or placebo.

Table 22: Asthma Exacerbation by Severity, Cohort, and Treatment Group for Placebo-Controlled Trials at 12 Weeks in Safety Cohort for Study 301 and Study 30017

ICS Cohort		Study 301			Study 30017		
		Placebo (N = 129)	FS MDPI 55 mcg/ 14 mcg b.i.d. (N = 128)	FS MDPI 113 mcg/ 14 mcg b.i.d. (N = 126)	Placebo (N = 144)	FS MDPI 113 mcg/ 14 mcg b.i.d. (N = 143)	FS MDPI 232 mcg/ 14 mcg b.i.d. (N = 145)
Patients with at least 1 asthma exacerbation, n (%)		7 (5)[a]	3 (2)	1 (< 1)	23 (16)	3 (2)	6 (4)
Severity	Mild	0	2 (2)	0	3 (2)	1 (< 1)	1 (< 1)
	Moderate	7 (5)	1 (< 1)	1 (< 1)	19 (13)	1 (< 1)	3 (2)
	Severe	0	0	0	1 (< 1)	1 (< 1)	2 (1)
	Missing	0	0	0	0	0	0
Patients with at least 1 asthma exacerbation resulting in hospitalization or discontinuation		4 (3)	1 (< 1)	0	19 (13)	1 (< 1)	4 (3)
Severity	Mild	0	0	0	3 (2)	0	0
	Moderate	4 (3)	1 (< 1)	0	16 (11)	0	2 (1)
	Severe	0	0	0	0	1 (< 1)	2 (1)
	Missing	0	0	0	0	0	0

b.i.d. = twice daily; FS MDPI = fluticasone propionate / salmeterol xinafoate multidose dry powder inhaler; n = number of patients with characteristic; N = total number of patients.

[a] The denominator for calculating percentages for severity is the number of patients with an asthma exacerbation. Patients with more than one exacerbation were counted at their highest level of severity.

Source: Clinical study reports.[3, 4]

2.3.2 Study 305

For Study 305, 463 patients (69%) across all treatment arms experienced at least one AE during the study (Table 23). The incidence of patients reporting treatment-emergent AEs across treatment arms FS MDPI and FS DPI were similar (70% in FS MDPI arms and 69%

in FS DPI arms). No deaths were observed during the study. The most common AEs across all treatment arms were upper respiratory infection, nasopharyngitis, sinusitis, cough, and oropharyngeal pain. Details of these AEs can be found in Table 31 (Appendix 3).

Approximately one-third of patients experienced mild and moderate AEs, respectively, while fewer than 10% of patients experienced severe AEs. Severe AEs included:

- pneumonia (three patients: two treated with FS MDPI 232 mcg/14 mcg, one treated with FS DPI 500 mcg/50 mcg)
- bronchitis (three patients: one treated with Fp MDPI 113 mcg, one treated with Fp MDPI 232 mcg, and one treated with FS MDPI 232 mcg/14 mcg)
- nausea (two patients: one treated with FS MDPI 113 mcg/14 mcg, and one treated with FS MDPI 232 mcg/14 mcg)
- asthma (18 patients: four treated with Fp MDPI 113 mcg, four treated with Fp MDPI 232 mcg, three treated with FS MDPI 113 mcg/14 mcg, five treated with FS MDPI 232 mcg/14 mcg, and two treated with FS DPI 500 mcg/50 mcg).

Table 23: Summary of Adverse Events in 26-Week Safety Study

Adverse Events, n (%)	FS MDPI 113 mcg/ 14 mcg b.i.d. (N = 120)	FS DPI 250 mcg/ 50 mcg b.i.d. (N = 41)	FS MDPI 232 mcg/ 14 mcg b.i.d. (N = 133)	FS DPI 500 mcg/ 50 mcg b.i.d. (N = 44)
TEAE	92 (77)	29 (71)	86 (65)	30 (68)
Severe TEAE	8 (7)	1 (2)	12 (9)	3 (7)
Serious TEAE	6 (5)	2 (5)	12 (10)	3 (7)
WDAE	3 (3)	2 (5)	0	1 (2)

b.i.d. = twice daily; FS DPI = fluticasone propionate / salmeterol xinafoate dry powder inhaler; FS MDPI = fluticasone propionate / salmeterol xinafoate multidose dry powder inhaler; n = number of patients with characteristic; N = total number of patients; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event.

Source: Clinical study report.[5]

Asthma exacerbation was recorded separately as an AE if it met the criteria of being severe (requiring systemic corticosteroid use for ≥ three days, or hospitalization or an emergency department visit requiring treatment with systemic corticosteroids).

Within the ICS/LABA cohort, the incidence of asthma exacerbation regardless of severity was similar between patients treated with FS MDPI 113 mcg/14 mcg and those treated with FS DPI 250 mcg/50 mcg. When comparing treatment arms in the high-strength ICS/LABA cohort, the proportion of patients experiencing at least one asthma exacerbation was higher in the FS MDPI 232 mcg/14 mcg arm (20 patients [15%]) than in the FS DPI arm (three patients [7%]).

Table 24: Asthma Exacerbation by Severity, Cohort, Treatment Group, and Disposition of Patients in 26-Week Safety Study

ICS Cohort		Medium-Strength		High-Strength	
		FS MDPI 113 mcg/ 14 mcg b.i.d. (N = 120)	FS DPI 250 mcg/ 50 mcg b.i.d. (N = 41)	FS MDPI 232 mcg/ 14 mcg b.i.d. (N = 133)	FS DPI 500 mcg/ 50 mcg b.i.d. (N = 44)
Patients with at least 1 asthma exacerbation, n (%)		13 (11)	5 (12)	20 (15)	3 (7)
Severity	Mild	2 (2)	2 (5)	5 (4)	0
	Moderate	8 (7)	3 (7)	7 (5)	1 (2)
	Severe	3 (3)	0	8 (6)	2 (5)
Disposition	Permanently discontinued	0	0	1 (< 1)	1 (2)
	Hospitalization	0	0	2 (2)	0
	ED / urgent care visit	0	0	4 (3)	1 (2)

b.i.d. = twice daily; ED= emergency department; FS DPI = fluticasone propionate / salmeterol xinafoate dry powder inhaler; FS MDPI = fluticasone propionate / salmeterol xinafoate multidose dry powder inhaler; ICS = inhaled corticosteroid; n = number of patients with characteristic; N = total number of patients.

[a] The denominator for calculating percentages for severity is the number of patients with an asthma exacerbation. Patients with more than one exacerbation were counted at their highest level of severity.

Source: Clinical study report.[5]

3. Pharmacoeconomic Evaluation

3.1 Manufacturer-Submitted Cost Information

The price of FS MDPI and individual components currently available on the Ontario Drug Benefit formulary are listed in

Table 25.

Table 25: Cost Comparison of New Combination Product and Individual Components

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Use	Daily Drug Cost ($)
Fluticasone propionate / salmeterol xinafoate (FS MDPI, Arbesda RespiClick)	55 mcg/14 mcg 113 mcg/14 mcg 232 mcg/14 mcg	Multidose dry powder inhaler (60 actuations)	$61.0440 $73.0740 $103.7340	1 inhalation twice daily	$2.0348 $2.4358 $3.4578
Fluticasone propionate (Flovent HFA)	50 mcg 125 mcg 250 mcg	Pressurized aerosol inhaler (120-dose pack)	$24.3240 $41.9400 $83.8920	100 mcg to 500 mcg twice daily	$0.8108 $1.3980 $2.7964
Fluticasone propionate (Flovent Diskus)	250 mcg 500 mcg	Multidose dry powder inhaler (60-blister pack)	$41.9580 $64.2000	100 mcg to 500 mcg twice daily	$1.3986 $2.1400
Salmeterol xinafoate (Serevent Diskhaler)	50 mcg	Dry powder inhaler (60-disk pack) Dry powder inhaler (60-dose pack)	$56.6600 $58.7340	50 mcg twice daily	$1.8887 $1.9578
Total component cost (fluticasone propionate + salmeterol xinafoate)					$2.6987 to $4.7542

FS MDPI = fluticasone propionate / salmeterol xinafoate multidose dry powder inhaler; HFA = hydrofluoroalkane.

Note: Patents listed on the Patent Register for the components of FS MDPI: CA 2407051, expiry: June 23, 2021; CA 2552468, expiry: June 23, 2021; and CA 2407262, expiry: June 23, 2021.

Source: Drug prices based on the Ontario Drug Benefit formulary (2017).[17]

Table 26: Cost Comparison Table

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Use	Average Daily Drug Cost ($)[a]
Fluticasone propionate / salmeterol xinafoate MDPI (Arbesda RespiClick)	55 mcg/14 mcg 113 mcg/14 mcg 232 mcg/14 mcg	Multidose dry powder inhaler (60 actuations)	$61.0440 $73.0740 $103.7340	1 inhalation twice daily	$2.0348 to $3.4579
Fluticasone propionate / salmeterol xinafoate HFA (Advair HFA)	125 mcg/25 mcg 250 mcg/25 mcg	Metered-dose inhaler (120 pack)	$99.0360 $140.5920	2 inhalations twice daily	$3.3012 to $4.6864
Fluticasone propionate / salmeterol xinafoate DPI (Advair Diskus)	100 mcg/50 mcg 250 mcg/50 mcg 500 mcg/50 mcg	60-dose pack	$82.7340 $99.0360 $140.5920	1 inhalation twice daily	$2.7578 to $4.6864
Fluticasone furoate / vilanterol (Breo Ellipta)	100 mcg/25 mcg 200 mcg/25 mcg	30-dose pack	$82.2000 $128.7400	1 inhalation once daily	$2.7400 to $4.2913
Budesonide / formoterol fumarate (Symbicort Turbuhaler)	100 mcg/6 mcg 200 mcg/6 mcg	120-dose pack	$66.8200 $86.8300	1 to 2 inhalations, once to twice daily	$2.2273 to $2.8943
Mometasone furoate / formoterol fumarate (Zenhale)	50 mcg/5 mcg 100 mcg/5 mcg 200 mcg/5 mcg	120-dose pack	$92.2560 $111.8160	2 inhalations twice daily	$3.0752 to $3.7272

DPI = dry powder inhaler; HFA = hydrofluoroalkane; MDPI = multidose dry powder inhaler.

[a] Average daily drug cost based on product monograph dosing.

Source: Product monographs[39-41] and Ontario Drug Benefit formulary accessed on June 29, 2017.[42]

3.2 Manufacturer-Submitted Information Regarding Current Patent Status

The following patents and patent expiration dates apply to FS MDPI:

- CA 2407501, expiry: June 23, 2021
- CA 2552468, expiry: June 23, 2021
- CA 2407262, expiry: June 23, 2021.

3.3 Critical Appraisal of Cost Information

The manufacturer presented a cost comparison of FS MDPI fixed-dose combination with the combined prices of currently reimbursed Fp and salmeterol xinafoate products. The manufacturer reported that at the submitted, dose-dependent prices of FS MDPI, the daily cost ranged from $2.03 to $3.46 based on recommended dosing schedules, resulting in cost savings of $0.66 to $1.30 per day when compared with the daily drug costs of Fp and salmeterol xinafoate used as individual components.

In the time since the manufacturer compiled its dossier for CADTH, the public prices for the individual Fp products have increased based on a review of the Ontario Drug Benefit formulary (

Table 25), resulting in additional cost savings for FS MDPI when compared with the combined cost of its individual components ($0.76 to $1.35 per day). Additionally, there is an ongoing review for an alternate Fp product (Fp MDPI; Aermony RespiClick). If the reimbursed price of Fp MDPI is less than that of the Fp used in the comparison, then FS

MDPI may become more costly than the individual components. The prices of the individual components listed in

Table 25 and Table 27 are based on publicly available information from the Government of Ontario and do not consider confidential negotiated prices. The submitted cost comparison does not consider variation across jurisdictions (Delta PA database, May 7, 2018).[43] When the lowest and highest public drug plan listed costs are used for Fp and salmeterol xinafoate, daily cost savings from FS MDPI range from $0.55 to $1.69.

Table 27: Cost Comparison of New Combination Product and Individual Components With Updated Drug Prices

Drug / Comparator	Strength	Dosage Form	Price per Pack ($)	Recommended Daily Use	Daily Drug Cost ($)
Fluticasone propionate / salmeterol xinafoate (Arbesda RespiClick)	55 mcg/14 mcg 113 mcg/14 mcg 232 mcg/14 mcg	Multidose dry powder inhaler (60 actuations)	$61.0440 $73.0740 $103.7340	1 inhalation twice daily	$2.03 $2.44 $3.46
Fluticasone propionate (Flovent HFA)	50 mcg 125 mcg 250 mcg	Pressurized aerosol inhaler (120-dose pack)	24.8300 42.8200 85.6400	100 mcg to 500 mcg twice daily	$0.83 $1.43 $2.85
Fluticasone propionate (Flovent Diskus)	100 mcg 250 mcg 500 mcg	Multidose dry powder inhaler (60-blister pack)	24.8300[b] 42.8220 65.5400	100 mcg to 500 mcg twice daily	$0.83 $1.43 $2.18
Salmeterol xinafoate (Serevent Diskhaler)	50 mcg	Dry powder inhaler (60-disk pack) Dry powder inhaler (60-dose pack)	$56.6600 $58.7340	50 mcg twice daily	$1.89 $1.96
Total component cost (fluticasone propionate + salmeterol xinafoate)					$2.79 to $4.81

HFA = hydrofluoroalkane.

Source: All prices are from the Ontario Drug Benefit formulary (accessed May 3, 2018),[17] and do not include dispensing fees.

The manufacturer also submitted a table comparing the costs of FS MDPI with other ICS/LABA fixed-dose combinations, including budesonide/formoterol, mometasone furoate / formoterol, fluticasone furoate / vilanterol, and two other fluticasone propionate / salmeterol combination products, the FS DPI (Advair Diskus) and FS HFA (Advair HFA). The prices for other ICS/LABA fixed-dose combinations have also increased based on the Ontario Drug Benefit formulary (Table 28); however, the cost comparison results remained similar. The daily drug cost of currently available ICS/LABAs may vary by jurisdiction.[43] Despite some ICS/LABAs being less expensive in some jurisdictions, price ranges for most drugs, except budesonide/formoterol, are associated with higher daily drug costs than FS MDPI. In some jurisdictions, FS MDPI may provide greater cost savings over currently available ICS/LABAs than reported for Ontario.

CDR also presented the price range for budesonide/formoterol, as the manufacturer-provided range assumed two inhalations, twice daily, when the price range should include one inhalation, once daily, based on the product monograph-recommended dosing. The updated average daily drug cost ranged from $0.57 to $2.94; as a result, FS MDPI would

present an increase in drug acquisition costs when comparing its price range to that of budesonide/formoterol.

Table 28: Cost Comparison Table With Inhaled Corticosteroid and Long-Acting Beta2 Agonist Combination Products With Updated Drug Prices

Drug/Comparator	Strength	Dosage Form	Price per Pack ($)	Recommended Daily Use	Average Daily Drug Cost ($)
Fluticasone propionate / salmeterol xinafoate (Arbesda RespiClick)	55 mcg/14 mcg 113 mcg/14 mcg 232 mcg/14 mcg	Multidose dry powder inhaler (60 actuations)	$61.0440 $73.0740 $103.7340	1 inhalation twice daily	$2.03 to $3.46
Fluticasone propionate / salmeterol xinafoate (Advair HFA)	125 mcg/25 mcg 250 mcg/25 mcg	Metered-dose inhaler (120 pack)	$101.1000 $143.5200	2 inhalations twice daily	$3.37 to $4.78
Fluticasone propionate / salmeterol xinafoate (Advair Diskus)	100 mcg/50 mcg 250 mcg/50 mcg 500 mcg/50 mcg	60-dose pack	$84.4500 $101.1000 $143.5200	1 inhalation twice daily	$2.82 to $4.78
Fluticasone furoate / vilanterol (Breo Ellipta)	100 mcg/25 mcg 200 mcg/25 mcg	30-dose pack	$83.9200 $130.5400	1 inhalation once daily	$2.80 to $4.35
Budesonide / formoterol fumarate (Symbicort Turbuhaler)	100 mcg/6 mcg 200 mcg/6 mcg	120-dose pack	$67.9200 $88.2600	1 to 2 inhalations, once to twice daily	$0.57 to $2.94
Mometasone furoate / formoterol fumarate (Zenhale)	50 mcg/5 mcg 100 mcg/5 mcg 200 mcg/5 mcg	120-dose pack	$93.5520 $113.3760	2 inhalations twice daily	$3.12 to $3.80

HFA = hydrofluoroalkane.

Source: All prices are from the Ontario Drug Benefit formulary (accessed May 3, 2018),[17] and do not include dispensing fees.

The following issues for consideration regarding the cost comparison were noted by CDR pharmacoeconomic reviewers:

- The manufacturer conducted its comparison of FS MDPI to the product's individual components and other ICS inhaler combinations, based on an assumption of equivalent dosing across treatment strengths. FS MDPI is available at lower doses of Fp and salmeterol xinafoate than the individual component Fp and salmeterol xinafoate. The manufacturer has indicated that the respective low-, mid- and high-strength doses of Fp in the fixed-dose combination are equivalent to the individual Fp dose (e.g., 55 mcg in fixed-dose combination to 100 mcg in individual product; 113 mcg to 250 mcg, and 232 mcg to 500 mcg). As noted in the CDR critical appraisal (section 2.2), the efficacy for FS MDPI was assessed through placebo-controlled studies. The only study with an active comparator (FS DPI) was an open-label study designed as a safety study. This study also included an efficacy component; however, these noninferiority analyses that compared individual doses of FS MDPI to FS DPI appear to have been performed ad hoc and were not adjusted for multiplicity, which limits the interpretation of the comparative efficacy for the relevant dosages from this study. As a result, it is difficult to draw any definitive conclusions on comparative costs for each of the FS MDPI strengths, given the uncertainty associated with the comparative clinical effects and the paucity of data regarding the equivalent dosages of FS MDPI with the individual components.
- [redacted]

[redacted]

- The clinical expert consulted by CDR noted that it is possible that FS MDPI will be prescribed, or consumed by patients, at double the available doses to match other fluticasone propionate / salmeterol xinafoate fixed-dose combinations that are currently available. Should this be the case, it is possible that FS MDPI would no longer be a cost saving. It may lead to an increase in costs compared with the individual component medications and other ICS/LABA fixed-dose combinations.
- The comparative efficacy and dosing of FS MDPI compared with other ICS/LABA fixed-dose combinations is uncertain. Thus, it is difficult to draw any definitive conclusions about the comparative costs of FS MDPI with ICS/LABA fixed-dose combinations.
- CDR notes that the use of FS MDPI may lead to savings on dispensing fees per claim when compared with the individual combination of its individual component medications.

Discussion

Summary of Available Evidence

Three multi-centre, parallel-group, phase III randomized controlled trials have been discussed in this review. Two of these studies (Study 301 and Study 30017) were double-blind placebo-controlled trials and one study (Study 305) was an active-controlled, open-label safety trial. The two efficacy trials evaluated the superiority of FS MDPI at 55 mcg/14 mcg, 113 mcg/14 mcg and 232 mcg/14 mcg twice daily compared with Fp MDPI at 55 mcg, 113 mcg and 232 mcg twice daily, or placebo. The active-controlled study was a 26-week safety study; it also evaluated the noninferiority of the pooled arms of FS MDPI 113 mcg/14 mcg and 232 mcg/14 mcg twice daily compared with the pooled arms of FS DPI 250 mcg/50 mcg and 500 mcg/50 mcg twice daily with respect to one efficacy outcome. All trials included patients who were ≥ 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 prior to consent being given.

In both 12-week efficacy trials, there were a higher number of withdrawals in the placebo arms than in the FS MDPI arms. These 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 among 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 comparative dosing, efficacy, and safety versus other ICS/LABA products.

The age of trial participants 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 more. The median pre-bronchodilator FEV_1, at screening ranged from 1.98 L to 2.71 L between treatment arms. According to the clinical expert consulted in this review, the patients recruited in the two placebo-controlled trials appeared to have suboptimal control of asthma relative to the Canadian population at the point of randomization, which may affect its generalizability.

Two additional studies, one phase I pharmacokinetic and one phase II dose-ranging, were summarized in Appendix 4 as supplemental information.

Interpretation of Results

Efficacy

With respect to lung function, both placebo-controlled studies demonstrated superiority of FS MDPI to Fp MDPI and to placebo in change from baseline in trough FEV_1 at week 12. Both of these studies evaluated the FS MDPI 113 mcg/14 mcg dose, and one study each evaluated the FS MDPI 55 mcg/14 mcg and 232 mcg/14 mcg doses. In Study 301, the difference from placebo in change from baseline in trough FEV_1 for FS MDPI 55 mcg/14 mcg twice daily was 0.266 L (95% CI, 0.172 to 0.360; *P* = 0.0000); for FS MDPI 113 mcg/14 mcg twice daily, it was 0.262 L (95% CI, 0.168 to 0.356; *P* = 0.0000). In Study 30017, the difference from placebo in trough FEV_1 for FS MDPI 113 mcg/14 mcg twice daily was 0.274 L (95% CI, 0.189 to 0.360; *P* = 0.0000) and for 232 mcg/14 mcg twice daily, it was 0.276 L (95% CI, 0.191 to 0.361; *P* = 0.0000). Little evidence is available on the MCID for FEV_1, yet the between-group differences were greater than the minimum patient perceivable improvement values reported in the literature (0.23 L)[3] as well as the MCID suggested by the Health Canada reviewer in the Fp MDPI report (0.20 L).[36] The Health Canada reviewer noted that the 0.20 L MCID may be more applicable for ICS (or ICS/LABA) treatment-naive patients. The sensitivity analyses supported the conclusions for this efficacy end point. Although comparisons versus Fp MDPI were statistically significantly in favour of FS MDPI, with between-group differences ranging from 0.092 L to 0.152 L, the clinical significance of the differences is uncertain.

The third open-label safety trial clearly stated that it was first and foremost a safety study. However, it reportedly had 90% power for demonstrating noninferiority of the pooled arms of FS MDPI 131 mcg/14 mcg and 232 mcg/14 mcg and the pooled arms of FS DPI 250 mcg/50 mcg and 500 mcg/50 mcg for change from baseline in trough FEV_1 over a 26-week treatment period, with a noninferiority margin pre-specified as −0.125 L. The treatment effect and lower limit of the 95% CI was found to have exceeded the −0.125 L noninferiority margin for the pooled arms of FS MDPI and FS DPI with regard to this outcome. (Least squares mean change: 0.029 L; 95% CI, 0.036, 0.095, *P* = 0.3821.)

The change in FEV_1 from baseline for Study 305 was lower than the changes observed in the efficacy studies, Study 301 and Study 30017. The clinical expert consulted for this review believes that this is likely due to the fact that during the run-in period of the placebo-controlled trials, patients were switched from their current asthma medication and placed on a low-dose ICS treatment.

In patient input, health-related quality of life measures were identified as outcomes important to patients (Appendix 2). AQLQ(S) was examined as a secondary outcome and administered only to patients 18 years and older. The evaluation included questions related to activity limitations, symptoms, emotional function, and environmental stimuli, with higher scores (the highest score being 32) correlating to a better health-related quality of life. When examining the change from baseline in the AQLQ(S) score at week 12 or the end point, there was a statistical difference observed in all FS MDPI arms compared with Fp MDPI or placebo. Firstly, the end point was used to denote the derived efficacy variable for week 12 with the last-observation carried forward imputation for missing data. Due to the high dropout rate in the placebo arm for Study 301 and Study 30017, the number of patients with

results for this outcome at week 12 was lower in the placebo arms than in the treatment arms. In Study 301, 75% of patients in the placebo arm had a value for AQLQ(S) at week 12 compared with 78% and 80% of patients in the FS 55 mcg/14 mcg and 113 mcg/14 mcg arms, respectively. In Study 30017, 70% of patients had a value for AQLQ(S) at week 12, compared with 90% and 85% for the FS MDPI 113 mcg/14 mcg and 232 mcg/14 mcg arms, respectively. All of the treatment arms, except for the FS MDPI 55 mcg/14 mcg arm in Study 301, achieved a mean change from baseline for a ≥ 0.5 score, which is the approximate MCID threshold to be considered clinically significant. However, according to the clinical expert involved in this review, the 12-week duration of treatment was likely insufficient to appropriately assess a 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 within the efficacy studies. Although the manufacturer provided data on asthma exacerbations in the safety section of this report, this outcome was identified as a key efficacy outcome for both the review of Fp MDPI and FS MDPI (see the CDR review of Fp MDPI [Aermony RespiClick]). The incidence of severe asthma exacerbation was also low in the 12-week efficacy studies. In the 26-week safety study, however, asthma exacerbations that were recorded as AEs in patients treated with FS MDPI 113 mcg/14 mcg were similar to those treated with FS DPI 250 mcg/50 mcg (13 patients [11%] and five patients [12%], respectively) and higher in patients treated with FS MDPI 232 mcg/14 mcg twice daily than in those treated with FS DPI 500 mcg/50 mcg twice daily (20 patients [15%] and three patients [7%], respectively). Severe asthma exacerbations also occurred at a numerically higher frequency in the FS MDPI arms than in the FS DPI arms, although the differences were not statistically significant. The clinical importance of the exacerbation results is highly uncertain. None of the studies were designed to assess exacerbations as a primary outcome, despite prevention of asthma exacerbations being recognized by the American Thoracic Society / European Respiratory Society Task Force on clinical asthma trials and clinical practice as “as an important component of establishing ideal asthma control.” The task force also stated that “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.”[44] Study 301, Study 30017, and Study 305 were relatively too short in duration to adequately evaluate the rates of asthma exacerbations.[45] 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.

Asthma symptoms are recognized as important outcomes of the disease. The end point of the total daily asthma symptoms score was analyzed as the change from baseline in the weekly average over weeks 1 to 12. The total daily asthma symptoms score is an average of the daytime (zero to five) and nighttime (one to four) scores, with the higher score indicating worse symptoms. Results for change from baseline in the weekly average of the total daily asthma symptoms score over weeks 1 to12 in all treatment arms showed a significant treatment difference compared with placebo. Between-group differences between FS MDPI and Fp MDPI for the average of total daily asthma symptoms scores over one week were statistically significant in Study 30017 in each of the comparison arms. Within studies, the treatment arms were comparable at baseline. All treatment arms in Study 301 and Study

30017 showed a significant decrease compared with placebo with respect to change from baseline in the weekly average total daily number of inhalations of albuterol or salbutamol.

The open-label study, Study 305, examined resource consumption between treatment arms. Overall, the reported average amount of health care resource consumption was high across different areas of health care (Appendix 3, Table 33). Over the course of this 26-week study, 29% of patients (96 out of 333) reported an unscheduled or outpatient visit, 15% of patients (49 out of 333) reported an emergency department or urgent care visit, and 3% of patients (10 out of 333) reported a hospital visit. Notably, there was a higher proportion of patients with an emergency department or urgent care facility visit belonging to either of the FS MDPI arms (17% of patients [42 out of 249] in the FS MDPI arms versus 8% of patients [seven out of 84] in the FS DPI arms). As well, a higher proportion of patients hospitalized belonged to either of the FS MDPI arms (4% of patients [nine out of 249] in the FS MDPI arms versus 2% of patients [one out of 44] in the FS DPI arms). Concerns were raised by the clinical expert involved in this review about these results as they are much higher than the average of those observed among asthma patients in Canada, based on lived experience.

[redacted], which included phase II dose-response trials, along with two pivotal phase III efficacy trials (studies 301 and 30017) and one long-term safety trial (Study 305).[46] The phase II trials, studies 201 and 202, were dose-ranging trials designed to determine superiority in efficacy of Fp MDPI compared with placebo, both of which also included an active control Flovent Diskus arm. These phase II studies are summarized in the CDR review of Fp MDPI. FSS-201, summarized in this review report, was a dose-ranging study comparing FS MDPI with placebo, and also included an active control Advair Diskus arm.[47] This trial, as well as one phase I trial evaluating the pharmacokinetics of FS MDPI and Advair Diskus, is summarized in Appendix 4. The phase I trial demonstrated that after administration of high-strength doses of FS MDPI and Advair Diskus, the systemic exposure of fluticasone propionate was similar between both inhalers, and the systemic exposure of salmeterol xinafoate was approximately 20% to 50% lower in the FS MDPI inhaler. Study FSS-201 suggested that there were no statistically significant differences observed between the FS MDPI doses currently marketed and Advair Diskus 100mcg/50 mcg for change in standardized baseline-adjusted FEV_1 AUC over 12 hours post-dose over 12 weeks, but this does not necessarily indicate equivalence or noninferiority between these two products.[47] [redacted] Therefore, there remains a degree of uncertainty regarding the dose equivalency and efficacy equivalency of FS MDPI compared with Advair Diskus. Notably, FDA analysis of Study FSS-201 indicated that dosage similarity could be concluded between FS MDPI 113mcg/14 mcg and Advair 100mcg/50 mcg given the lack of statistical significance between the treatment groups for the primary outcome, and because the FEV_1 values were similar between Advair and FS 113mcg/14 mcg (0.245 L versus 0.249 L), with the smallest between-group difference (0.003 L; 95% CI [–0.032 L, 0.039 L]). As well, the product monograph for FS 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 then switch to the respective starting doses, which are the low (55 mcg), medium (113 mcg), and high (232 mcg) doses of FS 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 component of FS MDPI 55 mcg, 113 mcg, or 232 mcg) they were randomized to in the phase III clinical trials.

In the absence of adequate head-to-head trial data for FS 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 randomized controlled trials to compare the efficacy of FS MDPI against other similar treatments currently available.[48] The indirect comparison was summarized and critically appraised in the CDR review of Fp MDPI. The primary outcomes in this study were FEV_1, FEV_1 AUC_{0-}, 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 FS MDPI.

Harms

The incidence of AEs in patients treated with FS MDPI was similar across studies. Serious AEs were rare (< 8% across studies) and did not suggest any association with specific treatments. One death was reported due to fulminant liver failure, in Study 30017.

The incidence of AEs was similar across treatment arms. The most common AEs reported in any treatment arm were nasopharyngitis, headache, upper respiratory tract infection, oral candidiasis, and cough, occurring in 3% or more subjects in any treatment group. With respect to oral candidiasis, there was a slightly higher incidence reported in the FS MDPI 113 mcg/14 mcg arm and 232 mcg/14 mcg arm (both 2%). The clinical expert involved in this study believed that this effect is typically dose-related. However, the studies were not sufficiently designed and were too short in duration to be able to assess key AEs usually considered with ICS/LABA products, such as pneumonia (ICS component) and cardiovascular events (LABA component).

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.

Cost

The manufacturer reported that at a daily cost ranging from $2.03 to $3.46 based on recommended dosing, FS MDPI is less costly compared with the daily drug costs of Fp and salmeterol xinafoate used as individual components, and may be less costly when compared with other ICS/LABA fixed-dose combinations except when compared with the budesonide/formoterol combination.

It was noted that the comparisons were based on public list prices, and if alternative pricing arrangements exist, the results of the cost comparisons may differ. Additionally, the clinical expert consulted for this review indicated that there is the potential for prescribers or patients

to double the number of actuations of FS MDPI per day to match their usual Fp dose. This would negate cost savings and could lead to increased costs. Finally, the critical appraisal of the manufacturer-provided information noted that the efficacy studies for FS MDPI were placebo controlled while the noninferiority analyses that compared individual doses of FS MDPI to an active comparator were from a safety trial that appeared to have been performed post hoc; the analyses were not adjusted for multiplicity. As a result, it is difficult to draw any definitive conclusions about the comparative costs, given the uncertainty associated with the comparative efficacy data and the paucity of data regarding the comparative doses for the individual strengths of FS MDPI.

Place in Therapy

Since the introduction of effective controller medications such as ICS, asthma mortality has decreased.[49] It has been shown that adding a LABA to low-dose ICS was more effective at preventing asthma exacerbations than was doubling the dose of ICS.[9] The use of ICS/LABA is now generally recommended as the next step in treatment for patients with persisting asthma symptoms despite low-dose ICS.[11] Asthma control in Canada, however, continues to be suboptimal. Statistics Canada describes asthma prevalence in those 12 and older of 8.4%.[1] Only 34.4% of Canadian were classified as having well-controlled asthma and 11.1% had at least one visit to a hospital emergency room in the previous year. Almost 40% of those surveyed did not understand why they had to take their medications, i.e., use a preventive medication for acute symptom control. Asthma control in Canada has not changed appreciably over a 10-year span despite increased numbers of ICS and ICS/LABA medications available for therapy.[50] Therefore, it is unlikely that one more ICS/LABA will appreciably improve asthma care in Canada. Fluticasone propionate / salmeterol xinafoate sold in Canada as Advair is one of the most expensive inhalers available to treat asthma. It is possible that less expensive ICS/LABA medications would improve accessibility of ICS/LABA 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.[51] The cost of medications is only one factor that impacts medication adherence and asthma control.

In general, ICS/LABA therapy is aimed at patients with moderate to severe asthma. The only tests required to identify patients who benefit from ICS/LABA is spirometry or bronchoprovocation testing to confirm the diagnosis of asthma. Subsequent evaluation includes the assessment of asthma control using questionnaire(s) and assessment of airflow obstruction using occasional spirometric testing or PEF monitoring. More detailed testing (induced sputum or exhaled nitric oxide) is typically reserved for patients who do not gain control with ICS/LABA therapy. FS MDPI (Arbesda RespiClick) does not fill an unmet clinical need in Canada as Canadians with moderate to severe asthma already have access to Advair as metered-dose inhaler or DPI formulations.

Conclusions

Three parallel-group RCTs were discussed in this review, which recruited patients 12 years and older with asthma, who were inadequately controlled on ICS. Patients were included in studies in which two different doses of Fp MDPI were compared against Fp MDPI, placebo, or FS DPI, for a minimum of 12 weeks and up to 26 weeks. There is very little comparative evidence for the use of FS MDPI versus alternative ICS/LABA combination therapies. Consequently, no concrete conclusions can be drawn with respect to the comparative effects of FS MDPI on asthma exacerbations. Supportive data from one phase

II dose-ranging study suggested no statistically significant difference in standardized baseline-adjusted FEV_1 AUC over 12 hours post-dose between medium-dose Advair Diskus and the currently marketed FS MDPI 113 mcg/14 mcg dose; though, this does not necessarily mean the FS products are equivalent or noninferior to each other. FS MDPI was found to be significantly superior to placebo with respect to lung function. Results from the phase III efficacy studies suggest that compared with placebo, FS MDPI 55 mcg/14 mcg, 113 mcg/14 mcg, and 232 mcg/14 mcg improved FEV_1, reduced the incidence of worsening asthma, and increased the number of days without asthma symptoms throughout 12 weeks. FS MDPI was also associated with statistically significant differences in asthma quality of life with standardized activities and use of rescue medication when compared against placebo; however, these results are limited by their short duration and incomplete data sets.

No rigorous assessment of patient preferences regarding the 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/LABA in patients with asthma, the submitted data do not provide evidence for long-term effects of FS MDPI; longer-term comparative studies would be useful to elucidate the benefits and harms of FS MDPI beyond 26 weeks of exposure.

At the submitted prices for each dose strength, FS MDPI would represent cost savings ranging from $0.66 to $1.30 per day when compared with the total daily drug costs of the individual component medications. FS MDPI would also represent cost savings when compared with most other ICS/LABA inhalers, though it is difficult to draw any definitive conclusions on the comparative costs, given the uncertainty associated with the comparative efficacy data and the paucity of data regarding the comparative doses for the individual strengths of FS MDPI with other ICS/LABA inhalers.

Appendix 1: Drug Plan Listing Status for Individual Components

For each indication that is approved by Health Canada for the new combination products (or likely to be approved, in the case of a submission filed on a pre-Notice of Compliance basis), please provide the publicly available listing status and criteria for the individual components of the combination product as well as other relevant comparators. CADTH may update the information provided by the manufacturer with new information provided by the CDR-participating drug plans, as required.

Step 1: Use a separate table for each indication being reviewed by CDR.

Step 2: Add the non-proprietary names for each individual component to the "Components" column and use a separate row for each component of the new combination product.

Step 3: Use the following abbreviations to complete the table.

Abbreviation	Description
EX	Exception item for which coverage is determined on a case-by-case basis
FB	Full benefit
NB	Not a benefit
RES	Restricted benefit with specified criteria (e.g., special authorization, exception drug status, limited-use benefit)
UR	Under review
–	Information not available

Table 29: Listing Status for Individual Components of the New Combination Product

Components	CADTH Common Drug Review-Participating Drug Plans													
	BC	AB	SK	MB	ON	NB	NS	PE	NL	YK	NT	NIHB	DND	VAC
Fluticasone propionate (Flovent)	FB	FB	FB	FB	FB	FB	FB	FB	FB	FB	FB	FB	FB	FB
Salmeterol xinafoate (Serevent)	RES	FB	RES	FB	RES	RES	RES	RES	RES	RES	RES	RES	RES	FB

AB = Alberta; BC = British Columbia; DND = Department of National Defence; FB = full benefit; MB = Manitoba; NB = New Brunswick; NIHB = Non-Insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; RES = Restricted benefit with specified criteria (e.g., special authorization, exception drug status, limited-use benefit); SK = Saskatchewan; VAC = Veterans Affairs Canada; YK = Yukon.

Step 4: For all restricted benefit entries, please state the criteria used by each drug plan. Use a separate table for each indication and add or delete rows as necessary.

Table 30: Restricted Benefit Criteria for Salmeterol Xinafoate for the Treatment of Asthma

Drug Plan	Criteria for Restricted Benefit
British Columbia	Diagnosis of asthma **plus** inadequate response on optimal dose of inhaled corticosteroid.
Saskatchewan	For the treatment of asthma uncontrolled on concurrent inhaled steroid therapy. It is important that these patients also have access to a short-acting beta2 agonist for symptomatic relief.
Ontario	For the treatment of asthma in patients who are using optimum anti-inflammatory treatment and are still experiencing breakthrough symptoms. Note: This drug is not for the relief of acute symptoms.
New Brunswick	For the treatment of patients with reversible obstructive airway disease who are using optimal corticosteroid treatment, but are still poorly controlled.
Nova Scotia	For the treatment of moderate to severe asthma in patients who: • Are compliant with ICSs at optimal doses • Require additional symptom control for various reasons (e.g., cough, awakening at night, missing activities such as school, work, or social activities because of asthma symptoms) • Require increasing amounts of short-acting beta2 agonists, indicative of poor control.
Prince Edward Island	For the treatment of asthma when used in patients on concurrent steroid therapy. Note: Patients using this product must also have access to a short-acting beta2 agonist bronchodilator for the relief of acute symptoms.
Newfoundland	For the treatment of moderate to severe asthma in patients who are: • Compliant with ICSs at optimal doses • Require additional symptom control for various reasons (e.g., cough, awakening at night, missing activities such as school, work, or social activities because of asthma symptoms) • Require increasing amounts of short-acting beta2 agonists, indicative of poor control.
Non-Insured Health Benefits Program	Limited-use benefit (prior approval required). For the treatment of asthma in patients who are using optimal corticosteroid therapy and experiencing breakthrough symptoms requiring regular use of a rapid-onset, short-duration bronchodilator.
Northwest Territories	Limited-use benefit (prior approval required). For the treatment of asthma in patients who are using optimal corticosteroid therapy and experiencing breakthrough symptoms requiring regular use of a rapid-onset, short-duration bronchodilator. Note: Aligned with NIHB.
Department of National Defence	Requests for special authorization are considered for members in the following situations: • Have a diagnosis of asthma which is uncontrolled, despite adherence to a low dose of ICSs OR • Have been prescribed treatment by a respirologist.
Yukon	For patients not adequately controlled on anti-inflammatory treatment.

Sources: Restricted benefit criteria for individual provincial formularies accessed during November 2017.[52-62]

Appendix 2: Summary of Patient Input

1. Brief Description of Patient Groups Supplying Input

Three patient groups — Asthma Canada, The Lung Association — Ontario, and British Columbia Lung Association 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 Canada, Sanofi Pasteur, Merck Canada, and Novartis in the past two years totalling in excess of $50,000.

BCLA is a registered charity that supports and promotes those living with or caring for others with lung disease, including asthma. Similar to TLA–O, it is also part of a federated model that works with the Canadian Lung Association and Canada's nine other provincial lung associations. BCLA has received financial support from Boehringer Ingelheim and AstraZeneca Canada in the past two years totalling $80,000. It has not received funding from Teva Canada Innovation, the producer of this drug under review.

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 that were sourced for the purposes of this submission
- a requested medical briefing provided by Teva Canada Innovation.

The online survey was sent to ACMA members in July 2017 and 88 responses were received. A total of 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 with asthma. With regard to the phone interviews, one was with a woman in her 50s who has had chronic severe asthma for 22 years, and the other was with a woman in her 30s who has had asthma for 10 years. Both patients indicated that their asthma symptoms were particularly bad this year. Characteristics of the people responding to the online surveys were not reported.

Information from BCLA was gathered in Canada in 2016 through a survey and shared experiences of patients with asthma.

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. They may experience an emotional burden (e.g., fear, stress, anxiety) or financial impact (e.g., time off work) or both 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 that current treatment options for the management of asthma symptoms include a combination of long-term controller medications (i.e., ICSs, long-acting bronchodilators, and leukotriene receptor antagonists) and fast-acting reliever medications for acute symptoms (i.e., short-acting bronchodilators). It was reported that patients also received systemic corticosteroids and biologics therapies (anti-immunoglobulin E and anti-interleukin 5 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, which include fatigue, shortness of breath, cough, low energy, poor appetite, and the inability to fight infection. TLA–O, however, reported several AEs associated with current treatments, including hoarse voice, increased mucus, low energy / fatigue, appetite loss, and an impact on mood. Both patient groups also acknowledged the cost burden of current treatments, as well as the intensive time requirements with regard to medical appointments.

Asthma Canada highlighted an unmet need with existing asthma medication. In particular, there is an important need for medicines that will improve symptom control, halt the progression of asthma, and prevent (or reduce) associated hospitalizations. It reported the need for therapies that will help patients to "live life to the fullest every day without fear of an exacerbation." Patients interviewed by TLA–O and BCLA reiterated that an ideal treatment would improve quality of life and 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

Some patients in the BCLA submission reported being in the clinical trial for this drug. In feedback, these patients stated that the inhaler device was “easier to use” and also “cheaper than what they were presently taking.” With respect to symptom control, patients involved in the clinical trial stated they were “able to breathe easily, and do chores they were not able to perform or do before.”

In the ACMA survey, two of 75 respondents had used Arbesda RespiClick (ICS/LABA) as part of a clinical trial or through other means. Both patients reported that ease of use and consistent, active metering would be a helpful option to patients with asthma.

No patients within the TLA–O submission reported having used fluticasone propionate.

ACMA survey participants were asked for their impressions on the potential availability of an “ICS/LABA inhaler that follows a simple, three-step process that administers a consistent low dose, and includes active metering, such as fluticasone propionate/salmeterol xinafoate.” Responses from survey participants indicated that this inhaler would be expected to improve the lives of people with asthma. Eighty per cent of respondents said they would be more likely to take their medication regularly if it had these characteristics.

Appendix 3: Additional Safety Tables

Table 31: Treatment-Emergent Adverse Events by Various Criteria for Events Reported for at Least 3% of Patients in Any Group (Safety Population) — Study 305

	ICS Cohort				ICS/LABA Cohort			
	Medium-Strength		High-Strength		Medium-Strength		High-Strength	
System Organ Class MedDRA 17.0 Preferred Term, 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)	FS MDPI 113 mcg/ 14 mcg b.i.d. (N = 120)	FS DPI 250 mcg/ 50 mcg b.i.d. (N = 41)	FS MDPI 232 mcg/ 14 mcg b.i.d. (N = 133)	FS DPI 500 mcg/ 50 mcg b.i.d. (N = 44)
Patients with at least 1 TEAE	85 (67)	29 (69)	83 (66)	29 (71)	92 (77)	29 (71)	86 (65)	30 (68)
Gastrointestinal disorders	14 (11)	6 (14)	7 (6)	5 (12)	18 (15)	3 (7)	13 (10)	5 (11)
Nausea	2 (2)	1 (2)	2 (2)	1 (2)	5 (4)	0	3 (2)	0
Vomiting	1 (< 1)	2 (5)	1 (< 1)	0	4 (3)	0	3 (2)	0
Toothache	1 (< 1)	0	1 (< 1)	2 (5)	0	0	1 (< 1)	0
General disorders and administration site conditions	9 (7)	2 (5)	9 (7)	2 (5)	9 (8)	2 (5)	9 (7)	5 (11)
Pyrexia	3 (2)	1 (2)	3 (2)	0	3 (3)	0	3 (2)	3 (7)
Infections and infestations	70 (55)	24 (57)	53 (42)	24 (59)	61 (51)	22 (54)	63 (47)	25 (57)
Upper respiratory tract infections	23 (18)	12 (29)	17 (14)	8 (20)	21 (18)	9 (22)	24 (18)	6 (14)
Sinusitis	15 (12)	3 (7)	6 (5)	3 (7)	9 (8)	4 (10)	14 (11)	8 (18)
Nasopharyngitis	17 (13)	7 (17)	13 (10)	5 (12)	15 (13)	4 (10)	12 (9)	4 (9)
Bronchitis	5 (4)	3 (7)	5 (4)	1 (2)	4 (3)	1 (2)	7 (5)	1 (2)
Oral candidiasis	6 (5)	0	5 (4)	5 (12)	5 (4)	2 (5)	5 (4)	5 (11)
Acute sinusitis	1 (< 1)	0	2 (2)	1 (2)	2 (2)	1 (2)	4 (3)	0
Urinary tract infection	3 (2)	0	2 (2)	2 (5)	2 (2)	0	4 (3)	1 (2)
Influenza	10 (8)	2 (5)	8 (6)	5 (12)	7 (6)	2 (5)	3 (2)	1 (2)
Gastroenteritis viral	0	1 (2)	1 (< 1)	2 (5)	2 (2)	1 (2)	2 (2)	1 (2)
Viral upper respiratory tract infection	1 (< 1)	1 (2)	3 (2)	0	4 (3)	2 (5)	1 (< 1)	1 (2)
Gastroenteritis	3 (2)	2 (5)	1 (< 1)	0	2 (2)	0	0	1 (2)
Injury, poisoning, or procedural complications	13 (10)	2 (5)	8 (6)	7 (17)	10 (8)	6 (15)	10 (8)	1 (2)
Procedural pain	1 (< 1)	0	1 (< 1)	2 (5)	1 (< 1)	2 (5)	1 (< 1)	0
Investigations	2 (2)	3 (7)	2 (2)	2 (5)	4 (3)	1 (2)	6 (5)	1 (2)
Cortisol free	0	1 (2)	0	2 (5)	0	0	0	0

	ICS Cohort				ICS/LABA Cohort			
	Medium-Strength		High-Strength		Medium-Strength		High-Strength	
Urine decreased								
Musculoskeletal and connective tissue disorders	13 (10)	2 (5)	13 (10)	5 (12)	9 (8)	6 (15)	8 (6)	1 (2)
Back pain	1 (< 1)	0	1 (< 1)	3 (7)	1 (< 1)	2 (5)	3 (2)	0
Arthralgia	0	2 (5)	5 (4)	1 (2)	2 (2)	1 (2)	1 (< 1)	0
Myalgia	4 (3)	0	0	0	0	1 (2)	1 (< 1)	0
Pain in extremity	2 (2)	0	3 (2)	0	0	2 (5)	1 (< 1)	0
Nervous system disorders	11 (9)	4 (10)	10 (8)	1 (2)	14 (12)	5 (12)	7 (5)	3 (7)
Headache	5 (4)	2 (5)	6 (5)	1 (2)	9 (8)	4 (10)	3 (2)	2 (5)
Respiratory, thoracic, and mediastinal disorders	35 (28)	9 (21)	31 (25)	7 (17)	31 (26)	8 (20)	26 (20)	10 (23)
Asthma	6 (5)	5 (12)	4 (3)	0	3 (3)	1 (2)	9 (7)	2 (5)
Oropharyngeal pain	13 (10)	0	6 (5)	1 (2)	7 (6)	0	9 (7)	4 (9)
Cough	10 (8)	3 (7)	13 (10)	4 (10)	14 (12)	2 (5)	8 (6)	1 (2)
Dyspnea	1 (< 1)	0	1 (< 1)	0	0	0	3 (2)	2 (5)
Rhinitis allergic	1 (< 1)	0	2 (2)	1 (2)	7 (6)	3 (7)	2 (2)	0
Sinus congestion	1 (< 1)	3 (7)	3 (2)	0	2 (2)	2 (5)	2 (2)	1 (2)
Respiratory tract congestion	1 (< 1)	3 (7)	0	0	2 (2)	0	1 (< 1)	0
Nasal congestion	2 (2)	0	3 (2)	2 (5)	3 (3)	0	0	2 (5)

b.i.d. = twice daily; Fp HFA = fluticasone propionate hydrofluoroalkane; Fp MDPI = fluticasone propionate multidose dry powder inhaler; FS MDPI = fluticasone propionate / salmeterol xinafoate multidose dry powder inhaler; FS DPI = fluticasone propionate / salmeterol xinafoate dry powder inhaler; ICS = inhaled corticosteroid; ICS/LABA = inhaled corticosteroid and long-acting beta2 agonist; n = total number of patients; N = total number of patients; TEAE = treatment-emergent adverse event.

Source: Clinical study report.[5]

Table 32: Adverse Reactions with ≥ 3% Incidence with FS MDPI, and More Common than Placebo in Patients with Asthma, Study 301 and Study 30017 Pooled

Adverse Reaction	FS MDPI 55 mcg/14 mcg b.i.d. (N = 128) %	FS MDPI 113 mcg/14 mcg b.i.d. (N = 269) %	FS MDPI 232 mcg/14 mcg b.i.d. (N = 145) %	Placebo (N = 273) %
Infections and Infestations				
Nasopharyngitis	8.6	4.8	6.9	4.4
Oral candidiasis[a]	1.6	2.2	3.4	0.7
Musculoskeletal and Connective Tissue Disorders				
Back pain	3.1	0.7	0	1.8
Nervous System Disorders				
Headache	5.5	4.8	2.8	4.4
Respiratory Disorders				
Cough	2.3	3.7	0.7	2.6

b.i.d. = twice daily; FS MDPI = fluticasone propionate / salmeterol xinafoate multidose dry powder inhaler; n = total number of patients.

[a] Oral candidiasis includes oropharyngeal candidiasis, oral fungal infection, and oropharyngitis fungal.

Source: Clinical study reports.[3,4]

Table 33: Health Care Utilization Over 26 Weeks, Study 305

End Points	FS MDPI 113 mcg/ 14 mcg b.i.d. (n = 119)	FS DPI 250 mcg/ 50 mcg b.i.d. (n = 40)	FS MDPI 232 mcg/ 14 mcg b.i.d. (n = 130)	FS DPI 500 mcg/ 50 mcg b.i.d. (n = 44)
Patients With an Unscheduled or Outpatient Visit				
Patients with visit, n (%)	38 (32)	7 (18)	40 (31)	11 (25)
Number of visits	52	8	66	15
Mean (SD)	1 (0.6)	1 (0.4)	2 (0.9)	1 (0.7)
Median (range)	1 (1, 3)	1 (1, 2)	1 (1, 5)	1 (1, 3)
Patients With an Emergency Department or Urgent Care Facility Visit				
Patients with visit, n (%)	22 (18)	2 (5)	20 (15)	5 (11)
Number of visits	23	2	22	5
Mean (SD)	1 (0.2)	1 (0.0)	1 (0.3)	1 (0.0)
Median (range)	1 (1, 2)	1 (1, 1)	1 (1, 2)	1 (1, 1)
Patients With a Hospital Visit				
Patients with visit, n (%)	3 (3)	0	6 (5)	1 (2)
Number of visits	4	0	9	1
Mean (SD)	1 (0.6)	0	2 (0.8)	1 (-)
Median (range)	1 (1, 2)	0	1 (1, 3)	1 (1, 1)

b.i.d. = twice daily; FS DPI = fluticasone propionate / salmeterol xinafoate dry powder inhaler; FS MDPI = fluticasone propionate/salmeterol xinafoate multidose dry powder inhaler; n = total number of patients; SD = standard deviation.

Source: Clinical study report.[5]

Appendix 4: Summary of Phase I and II Studies

Introduction

To summarize the findings of two phase I and II studies, which assess the comparative pharmacokinetic, efficacy, and safety data of fluticasone propionate / salmeterol xinafoate multidose dry powder inhaler (FS MDPI) against products containing fluticasone propionate/salmeterol xinafoate that are already available.

Findings

Objectives and Rationale

The primary objective of the phase I study, Study 10042, was to determine the pharmacokinetics and tolerability of high-dose FS MDPI with high-dose Advair Diskus.[33,47,63]

The primary objectives of the phase II supportive study, Study FSS-201, were to evaluate the dose response and safety of four doses of FS MDPI versus both placebo and open-label Advair Diskus for the treatment of asthma.[47,63]

Study Design

Study 10042 was a phase I, multi-centre, open-label, randomized, active-controlled, four-period crossover, single-dose study (N = 40). [33,47]

The phase II supportive study, Study FSS-201, was a randomized, multi-centre, double-blind, open-label, active-controlled, single-dose, six-period crossover, dose-ranging study conducted in patients aged 12 years and older with persistent asthma. Patients had to have a best FEV_1 of 40% to 85% of predicted based on age, height, sex, and race, and demonstrate a post-bronchodilator reversibility of at least 15%. Fluticasone propionate multidose dry powder inhaler (Fp MDPI) and FS MDPI were administered in a double-blind manner and Advair Diskus was administered in an open-label manner. Prior to the run-in period of this study, patients discontinued current asthma medication, such as short-acting bronchodilators, inhaled corticosteroids (ICS), or other controller therapies. Patients were instructed to take two inhalations of Fp MDPI 50 mcg twice daily to replace current ICS treatment throughout the 14-day run-in period and each of the washout periods between treatments. Salbutamol hydrofluoroalkane was also provided to the patient as rescue treatment.[47,63]

Intervention and Comparators

The evaluated treatments for each of these studies are summarized in Table 34. The currently marketed FS MDPI product is the 100 mcg/12.5 mcg formulation. This dose is now referred to as FS MDPI 113 mcg/14 mcg to represent its metered dose per inhalation.

Table 34: Evaluated Treatments in Phase I and Phase II Studies

Study 10042	Study 201
Fp MDPI 232 mcg x 1 inhalation	Fp MDPI 100 mcg x 1 inhalation b.i.d.
FS MDPI 232 mcg/14 mcg x 1 inhalation	FS MDPI 100 mcg/6.25 mcg x 1 inhalation b.i.d.
Flovent Diskus 250 mcg x 2 inhalations	FS MDPI 100 mcg/12.5 mcg x 1 inhalation b.i.d.
Advair Diskus 500 mcg/50 mcg x 1 inhalation	FS MDPI 100 mcg/25 mcg x 1 inhalation b.i.d.
	FS MDPI 100 mcg/50 mcg x 1 inhalation b.i.d.
	Advair Diskus 100 mcg/50 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 xinafoate multidose dry powder inhaler, mcg = micrograms.
Source: Health Canada Reviewer's Report[64]; Common Technical Document.[47]

Outcomes

In Study 10042, the systemic levels of fluticasone propionate and salmeterol xinafoate 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 Study FSS-201, the primary end point was to evaluate the dose response of four different doses of salmeterol xinafoate, each combined with a fixed dose of fluticasone propionate, delivered as FS MDPI.

Statistical Analysis

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

The primary outcome analysis in Study 201 was defined as the area under the curve for baseline-adjusted FEV_1 measurements from the pre-dose to 12 hours post-dose time points based on actual time of measurement and was standardized by dividing the actual time of the last FEV_1 measurement. Baseline-adjusted FEV_1 was calculated as post-dose FEV_1 after subtracting period-specific baseline FEV_1. The period-specific baseline FEV_1 was measured at pre-dose within five minutes of the morning dose administration. If that value was missing, then FEV_1 measured at 30 minutes pre-dose was used as the period-specific baseline. The primary analysis was performed using an ANCOVA model with fixed effects of sequence, period, and treatment; a random effect of patient within sequence; and a covariate of period-specific baseline FEV_1. A fixed-sequence testing procedure was used to control the overall type I error rate at the two-sided 0.05 level of significance.

Study Populations

Study 10042

Study 10042 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 to 72 years). Fifty-six per cent of the patients were male, and 72% of the patients were white.

Study FSS-201

Study 201 was conducted in patients aged 12 years and older with persistent asthma. The mean age of patients was 42.5 years, with a range of 13 through 86 years. Forty-nine per cent of the patients were male, and 89% were white. A total of 72 patients were randomized, all of whom received at least one dose of the study drug, with 65 (90%) completing the study. Of the seven (10%) patients who withdrew, one withdrew for an adverse event (asthma exacerbation) during the washout period with Fp MDPI 50 mcg. All 72 randomized patients were included in the full analysis population used for the primary efficacy.

Results

Efficacy

The results for the primary efficacy outcome are displayed in Table 35. All FS MDPI doses had a statistically significantly higher standardized baseline-adjusted FEV_1 $AUC_{0\text{-}12h}$ compared with Fp MDPI 100 mcg. The primary efficacy outcome for FS 100 mcg/50 mcg was found to be statistically significantly higher than that in the Advair Diskus 100 mcg/50 mcg arm. The FS MDPI 100 mcg/12.5 mcg and 100 mcg/25 mcg arms were not found to be significantly different from the Advair Diskus arm for this efficacy outcome. The FS MDPI 100 mcg/12.5 mcg (113 mcg/14 mcg) arm is the currently marketed FS MDPI dose. This dose was chosen because of the similarity in least squares mean difference standardized baseline-adjusted FEV_1 $AUC_{0\text{-}12h}$ from baseline to week 12 values achieved as compared with Advair Diskus.

Table 35: Change in FEV_1 $AUC_{0\text{-}12h}$ (L) From Baseline to Week 12 by Treatment Group by Full Analysis Set in Study FSS-201

	Number (%) of Patients					
	Fp MDPI	FS MDPI				Advair Diskus 100 mcg/ 50 mcg b.i.d. (N = 66)
	100 mcg b.i.d. (N = 67)	100 mcg/6.25 mcg b.i.d. (N = 68)	100 mcg/ 12.5 mcg b.i.d. (N = 69)	100 mcg/25 mcg b.i.d. (N = 67)	100 mcg/ 50 mcg b.i.d. (N = 68)	
Baseline FEV_1 mean (SD)	2.308	2.293	2.313	2.346	2.282	2.309
LSMD standardized baseline-adjusted FEV_1 $AUC_{0\text{-}12h}$ from baseline to week 12	0.052	0.204	0.249	0.280	0.303	0.245
LSMD from Fp MDPI 100 mcg (95% CI)	–	0.152 (0.116 to 0.188)	0.197 (0.161 to 0.233)	0.228 (0.192 to 0.264)	0.251 (0.216 to 0.287)	0.193 (0.157 to 0.230)
LSMD from Advair Diskus 100 mcg/50 mcg b.i.d. (95% CI)	–0.193 (–0.230 to –0.157)	–0.042 (–0.078 to –0.006)	0.003 (– 0.032 to 0.039)	0.034 (–0.002 to 0.070)	0.058 (0.022 to 0.094)	–

B.i.d. = twice daily; CI = confidence interval; FEV_1 $AUC_{0\text{-}12h}$ = forced expiratory volume in one second from time 0 to 12 hours post-dose; Fp MDPI = fluticasone propionate multidose dry powder inhaler; FS MDPI = fluticasone propionate/salmeterol xinafoate multidose dry powder inhaler; LSMD = least squares mean difference; SD= standard deviation.

Source: FDA Medical Report.[33]

Pharmacokinetic Data

Study 10042

Study 10042 compared a high-strength dose of Advair Diskus with a high-strength dose of FS MDPI in patients with asthma. Pharmacokinetic results for this study are displayed on Table 36 by concentration of fluticasone propionate and salmeterol xinafoate, respectively. Regarding the concentration of fluticasone propionate, following a single-dose administration of FS MDPI (200 mcg/12.5 mcg x one inhalation) compared with Advair Diskus (500 mcg/50 mcg x one inhalation), the systemic exposure (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) to fluticasone propionate was similar between the two. Regarding the concentration of salmeterol xinafoate, the systemic exposure (maximum drug-plasma concentration and area under the curve) was ~20% to 50% lower with FS MDPI compared with Advair Diskus.

Table 36: Pharmacokinetics Descriptive Statistics in Phase I Study (10042)

Parameter	Treatment	N	Geometric LS Mean	GMR	90% CI
Fluticasone Propionate Pharmacokinetic Comparison					
AUC_{0-t} (pg▪h/mL) Mean (SD)	FS MDPI Advair Diskus	36 36	545.48 566.96	0.962	0.87 to 1.07
C_{max} (pg/mL) Mean (SD)	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)	FS MDPI Advair Diskus	28 28	586.85 618.51	0.949	0.86 to 1.04
Salmeterol Xinafoate Pharmacokinetic Comparison					
AUC_{0-t} (pg▪h/mL) Mean (SD)	FS MDPI Advair Diskus	35 35	119.65 241.22	0.496	0.46 to 0.54
C_{max} (pg/mL) Mean (SD)	FS MDPI Advair Diskus	35 35	56.50 69.71	0.811	0.70 to 0.94
$AUC_{0-\infty}$ (pg▪h/mL) Mean (SD)	FS MDPI Advair Diskus	34 34	134.38 262.69	0.511	0.47 to 0.55

$AUC_{0-\infty}$ = 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; CI = confidence interval; C_{max} = maximum measured concentration of analyte in plasma; 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.[33,34]

Study FSS-201

The pharmacokinetics of salmeterol were evaluated in this study. The mean plasma concentration of salmeterol was found to be highest at five minutes post-dose for each FS MDPI dose level. Both the AUC_{0-t} and C_{max} of salmeterol were found to increase with increasing dose of FS MDPI. Compared with Advair Diskus, the t_{max} in FS MDPI groups occurred earlier (median = 0.1 hour) than Advair Diskus (median = 0.5 hour). Only FS 100 mcg/50 mcg attained a mean plasma salmeterol xinafoate concentration that was greater than those obtained for Advair Diskus over 12 hours. FS MDPI 100 mcg/12.5 mcg, the currently marketed product, had similar clinical efficacy with a lower systemic exposure compared with 50 mcg of salmeterol in Advair Diskus.

Safety

No serious adverse events were reported in either supportive Study FSS-201 or Study 10047.

Conclusions

FS MDPI was compared with Advair Diskus, a product currently marketed in Canada with identical medicinal ingredients, in two studies. Study 10042 suggested that after administration of a high-strength dose of FS MDPI and Advair Diskus, the systemic exposure of fluticasone propionate was similar between both inhalers, and the systemic exposure of salmeterol xinafoate is approximately 20% to 50% lower with the FS MDPI inhaler. There was no statistically significant difference in standardized baseline-adjusted FEV_1 AUC over 12 hours post-dose between medium-dose Advair Diskus and the currently marketed FS MDPI 100 mcg/12.5 mcg dose, but this does not necessarily indicate equivalence or noninferiority between these two products. The systemic exposure of fluticasone propionate and salmeterol xinafoate is expected to be lower or similar to those components in Advair Diskus, with no statistically significant difference in efficacy outcomes.

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