A 6-month safety and efficacy study of fluticasone propionate and fluticasone propionate/salmeterol multidose dry powder inhalers in persistent asthma

Lyndon Mansfield, M.D.,[1] Gloria Yiu, M.S.,[2] Anat Sakov, Ph.D.,[3] Siyu Liu, M.D., Ph.D.,[4] and Cynthia Caracta, M.D., F.C.C.P.[5]

ABSTRACT

Background: *A novel multidose dry powder inhaler (MDPI) that is breath actuated, easy, and intuitive to use has been developed for administering fluticasone propionate (Fp) and Fp/salmeterol (FS).*

Objective: *To assess the safety and efficacy of Fp MDPI versus Fp hydrofluoroalkane (HFA) and FS MDPI versus FS dry-powder inhaler (DPI).*

Methods: *This phase III, 26-week, open-label, active drug–controlled study enrolled subjects ≥12 years old with persistent asthma. Based on entry controller medication (inhaled corticosteroid [ICS] or ICS/long-acting beta-agonist), the subjects were randomized to twice-daily mid-strength Fp MDPI 100 μg or Fp HFA 220 μg, high-strength Fp MDPI 200 μg or Fp HFA 440 μg, mid-strength FS MDPI 100/12.5 μg or FS DPI 250/50 μg, or high-strength FS MDPI 200/12.5 μg or FS DPI 500/50 μg in a 3:1 MDPI to Fp HFA or FS DPI ratio. Safety and efficacy were assessed by adverse events (AE) and pulmonary function and asthma symptoms, respectively.*

Results: *A total of 674 subjects were randomized. The AE incidence was similar across treatment groups (upper respiratory tract infections, sinusitis, and nasopharyngitis were most frequent). A higher percentage of subjects in the Fp HFA 440 μg and FS DPI 500/50 μg groups had oral candidiasis versus those who received Fp MDPI 200 μg or FS MDPI 200/12.5 μg, respectively. Serious AEs were similar between the treatments, with no unexpected findings. The incidence of asthma exacerbations was low and generally similar between the groups. Noninferiority was established for all Fp MDPI and FS MDPI doses compared with Fp HFA and FS DPI, respectively, for forced expiratory volume in 1 second. Changes in peak expiratory flow, rescue albuterol use, and symptoms were similar between treatments.*

Conclusion: *The safety and efficacy profiles of Fp MDPI and FS MDPI administered at lower doses were generally comparable with those of Fp HFA and FS DPI, respectively, after 26 weeks of treatment.*

(Allergy Asthma Proc 38:1–13, 2017; doi: 10.2500/aap.2017.38.4061)

The goals of pharmacotherapy of asthma are to control symptoms, preserve pulmonary function, and prevent asthma episodes and exacerbations.[1] Long-term asthma control may require daily doses of controller medications, *e.g.*, inhaled corticosteroids (ICS), or combination therapies, *e.g.*, ICS with a long-acting beta-agonist (LABA).[1] The safety of regular use of LABAs has been debated.[2] The most recent findings from the multicenter, randomized, double-blind AUSTRI trial of subjects with moderate-to-severe asthma found no greater risk of serious asthma-related events with ICS/LABA (fluticasone propionate [Fp] plus salmeterol [FS]) compared with ICS monotherapy (Fp).[2] Previous studies that found an increased risk of asthma-related deaths with LABAs did not control for ICS use.[3–6] In the AUSTRI trial, the ICS/LABA combination reduced the risk of severe asthma exacerbations by 21% compared with ICS monotherapy and provided significant clinical benefits.

Patients need to coordinate inhalation with device actuation for the maximal benefit from a pressurized metered dose inhaler.[7,8] Improper coordination limits optimal deposition of the medication in the lungs, which leads to less symptom control.[7,9–11] A novel, multidose dry powder inhaler (MDPI) (Teva Pharmaceuticals, Inc., Frazer, PA) has been developed that does not require coordination of actuation and inhala-

From the [1]Western Sky Medical Research, El Paso, Texas, [2]Global Statistics Department, Teva Pharmaceuticals, Frazer, Pennsylvania, [3]Global Statistics Department, Teva Pharmaceuticals, Netanya, Israel, [4]Global Patient Safety and Pharmacovigilance, Teva Pharmaceuticals, Frazer, Pennsylvania, and [5]Clinical Research, Global Respiratory R&D, Teva Pharmaceuticals, Frazer, Pennsylvania

This study was sponsored by Teva Branded Pharmaceutical Products R&D, Inc. Medical writing assistance was provided by Lisa Feder, Ph.D., Peloton Advantage, and was funded by Teva Branded Pharmaceutical Products R&D, Inc. Teva provided a full review of the article.

L. Mansfield is a consultant/adviser for Aimmune Therapeutics; G. Yiu and S. Liu are employees of Teva Pharmaceuticals, Frazer, PA; A. Sakov is an employee of Teva Pharmaceuticals, Netanya, Israel; and C. Caracta was an employee of Teva Pharmaceuticals, Frazer, PA, at the time of study conduct and manuscript preparation.

Poster presentation at the American College of Allergy, Asthma & Immunology annual meeting, San Francisco, California, November 10–14, 2016.

Address correspondence to Lyndon Mansfield, M.D., Western Sky Medical Research, 2121 Wyoming Avenue, El Paso, TX 79903

E-mail address: immunman@westernskymed.com

tion, and it is intuitive and easy to learn the correct use.[12] The device is inhalation driven and delivers the medication to the airways as a fine powder without using propellants. Multiple dosage strengths of Fp and FS using the MDPI are available. Analysis of pharmacokinetic data indicates that delivery by MDPI is more efficient and allows the use of lower doses of Fp and FS compared with currently available similar products.[12–14]

The effectiveness of lower doses was evaluated and confirmed in a 12-week dose-ranging study that demonstrated similar improvements in pulmonary function and a similar safety profile in subjects treated with Fp MDPI 25, 50, or 100 μg compared with Fp DPI 100 μg.[15] In another double-blind, single-dose, six-period crossover, dose-ranging study, FS MDPI 100/12.5 μg demonstrated similar efficacy compared with FS DPI 100/50 μg, which confirmed the ability to use a lower salmeterol dose with the MDPI to allow for less salmeterol exposure.[16] The objective of this study was to assess the 6-month safety of mid-strength Fp (100 μg) and FS (100/12.5 μg) and of high-strength Fp (200 μg) and FS (200/12.5 μg) delivered *via* the MDPI compared with Fp hydrofluoroalkane (HFA) (220 μg [mid-strength] and 440 μg [high-strength]) and FS dry-powder inhaler (DPI) (250/50 μg [mid-strength] and 500/50 μg [high-strength]), respectively, in adolescents and adults with persistent asthma.

METHODS

Study Description

This 26-week, stratified, randomized, open-label, active drug–controlled, phase III study (FSS-AS-305) assessed the 6-month safety and efficacy of Fp MDPI 100 and 200 μg administered twice daily (b.i.d.), FS MDPI 100/12.5 and 200/12.5 μg b.i.d., Fp HFA 220 and 440 μg b.i.d., and FS DPI 250/50 and 500/50 μg b.i.d. in subjects ages ≥12 years with persistent asthma. Written informed consent was signed by each subject and by the legally acceptable representative for minors. The study was conducted in accordance with International Council for Harmonisation Good Clinical Practice Consolidated Guideline (ICH/GCP E6) and all applicable national and local laws and regulations. The study protocol was submitted to the independent ethics committee or institutional review board and approved before study initiation. The ClinicalTrials.gov identifier is NCT02175771.

Subjects

Males and females who were not pregnant, ages ≥12 years, with a forced expiratory volume in 1 second (FEV_1) of ≥40% of predicted value for age, height, sex, and race (*i.e.,* persistent asthma as defined per National Health and Nutrition Examination Survey III values),[17] an established treatment regimen of a short-acting beta-agonist (SABA) (albuterol/salbutamol) for use as needed and either a mid- or high-dose ICS or ICS/LABA combination as preventive therapy for ≥8 weeks before the screening visit, demonstrated ≥12% reversibility of FEV_1 within 30 minutes after SABA HFA 90 μg administration at the screening visit, and the ability to replace existing SABA with albuterol/salbutamol HFA at screening for as-needed use during the study were included.

Exclusion criteria were treatment with a low-dose ICS without LABA, a history of life-threatening asthma exacerbation, an asthma exacerbation within 30 days of screening, hospitalization for asthma 2 months before screening, and use of immunosuppressive medications 4 weeks before screening. Planned initiation or dose escalation of immunotherapy during the study was not permitted. Other exclusion criteria were documented or suspected bacterial or viral infection within 2 weeks of screening; a history of a positive human immunodeficiency virus test result or active hepatitis B virus or hepatitis C virus infection; the presence of untreated oral candidiasis; and any illness that, in the judgment of the investigators, would put the subject at risk during the study. Current smokers, subjects with a ≥10-pack-year smoking history, subjects who used tobacco products within the past year, and those with a history of drug or alcohol abuse within 2 years of screening were not permitted to enroll in the study.

The subjects were randomized if they had an FEV_1 of ≥40% of predicted normal at treatment visit 1; no changes in asthma medications; no asthma exacerbations, upper respiratory infection, or lower respiratory tract infection during the 14-day run-in period; no clinically significant abnormal laboratory test results; a normal electrocardiogram (ECG) result; no visual evidence of untreated oropharyngeal candidiasis; and a completed daily asthma diary that included asthma symptom scores, rescue medication use, and peak expiratory flow (PEF) measurements on at least 4 of 7 days preceding randomization.

Study Design

The study subjects completed a 14-day (±2 days) run-in period and continued using their current asthma medications except for their replaced SABA. At randomization, the ICS or ICS/LABA medications were stopped and the subjects were assigned to an ICS or ICS/LABA cohort based on their entry asthma maintenance therapy. Within each of the two cohorts, the subjects were stratified into either mid- or high-strength treatment based on the dose of their current therapy; previous Fp HFA doses of >180 to 460 μg/day or equivalent were stratified to mid-strength, and doses of >460 μg/day were stratified to high-strength.

The subjects were then randomized in a 3:1 ratio between MDPI and the comparators for each cohort and dose strength. This scheme created eight treatment groups. Mid-strength ICS was Fp MDPI 100 μg, 1 inhalation b.i.d., or Fp HFA 220 μg, b.i.d.; high-strength ICS was Fp MDPI 200 μg, 1 inhalation b.i.d., or Fp HFA 440 μg, b.i.d.; mid-strength ICS/LABA was FS MDPI 100/12.5 μg, 1 inhalation b.i.d., or FS DPI 250/50 μg, 1 inhalation b.i.d.; and high-strength ICS/LABA was FS MDPI 200/12.5 μg, 1 inhalation b.i.d., or FS DPI 500/50 μg, 1 inhalation b.i.d. The subjects returned 2 weeks after randomization and then every 4 weeks for the study duration. Trough pulmonary function tests at 12 hours after taking the dose were obtained at each morning visit. The subjects continued to record daily PEF measurements, asthma symptom scores, and rescue medication use in daily asthma diaries.

Safety

Safety monitoring included physical examinations, laboratory evaluations, 12-lead ECGs, and recording of adverse events (AE). The primary safety measures were the incidence and type of AEs. An AE is defined as any untoward medical occurrence in a study subject administered a pharmaceutical product. Treatment-emergent AEs (TEAE) occurred after the first dose of study drug and until the end of the follow-up period. Investigators characterized the relationship of AEs to the study drug. Serious AEs (SAE) were defined by the International Council for Harmonisation/Good Clinical Practice criteria. Asthma exacerbations were defined as worsening of asthma that required additional treatment other than rescue albuterol (salbutamol) or the subject's study ICS or ICS/LABA treatment. A severe asthma exacerbation required systemic corticosteroids for ≥3 days or hospitalization or an emergency department visit that required systemic corticosteroids. Mild and moderate asthma exacerbations were defined by the investigator. A subset of the safety population was evaluated for 24-hour urinary cortisol testing at treatment visits 1, 5, and 8 (randomization, week 14, and week 26). Subjects with confounding factors (*e.g.,* low urine collection volume, low 24-hour creatinine excretion) were not analyzed in the subset.

Efficacy

The principal efficacy end point was the change from baseline in morning trough FEV_1 over the 26-week treatment period. Other end points included a change from baseline in forced vital capacity (FVC) and forced expiratory flow between 25% and 75% of the forced vital capacity ($FEF_{25–75}$), frequency and amount of rescue medication use, withdrawals due to worsening asthma symptoms, change in A.M. PEF, and change from baseline in asthma symptom scores.

Statistics

The safety population included all randomized subjects who received at least one dose of randomized study drug, and this population was used for all analyses of safety data. The full analysis set, including all randomized subjects who received at least one dose of study drug and had at least one postbaseline trough FEV_1 assessment, was used for all efficacy analyses.

For the primary safety analyses, AEs were coded using the Medical Dictionary for Regulatory Activities (International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, McLean, VA) preferred terms. All safety analyses were summarized using descriptive statistics. Analyses of efficacy end points were performed using the mixed method for repeated measures model with effects due to value of the measure at baseline, sex, age, investigational center, visit, treatment, and visit-by-treatment interaction. Baseline spirometry was the last assessment recorded before randomization. Data collected in daily diaries used the average daily data recorded in the 7 days before randomization for baseline (treatment visit 1). The model was used to estimate treatment means and treatment mean differences with two-sided 95% confidence intervals (CI) and p values between the MDPI and comparator products. For FEV_1, noninferiority would be demonstrated if the lower limit of the 95% CI for the treatment difference was greater than −125 mL based on the minimally perceivable improvement in asthma therapeutics.[18]

RESULTS

Subjects

A total of 1087 subjects were screened, and 674 subjects were randomized to treatment groups (Fig. 1). Demographic characteristics were similar across the treatment groups (Table 1). The mean age ranged from 38.4 to 46.1 years, and the mean baseline FEV_1 ranged from 2.31 to 2.70 L.

Safety Data

Overall, 463 subjects (69%) experienced at least one TEAE during the study (Table 2). The incidences of TEAEs, treatment-related TEAEs, serious TEAEs, and TEAEs that led to withdrawal were balanced within each treatment and dose cohort, with no evidence of dose or treatment dependence. The most frequently occurring TEAEs across all the treatment groups were upper respiratory tract infections (n = 120), nasopharyngitis (n = 77), sinusitis (n = 62), cough (n = 55), and oropharyngeal pain (n = 45). The majority of TEAEs

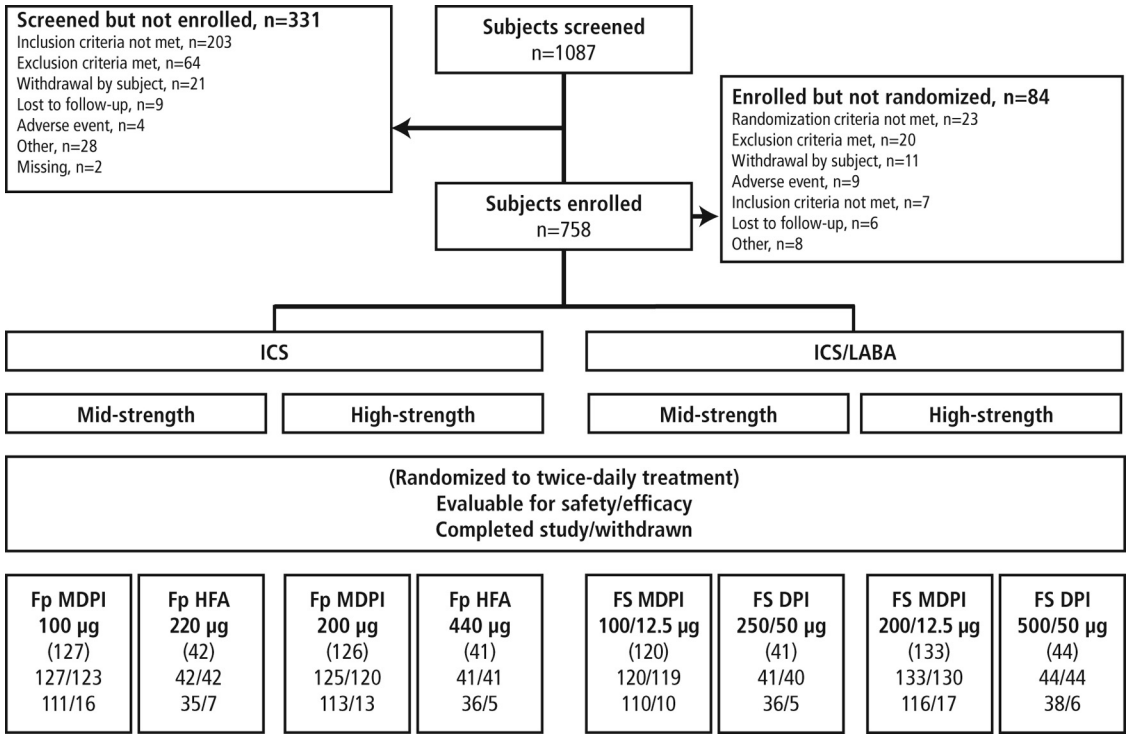

Figure 1. *Subject disposition. Fp HFA = Fluticasone propionate hydrofluoroalkane; Fp MDPI = fluticasone propionate multidose dry powder inhaler; FS DPI = fluticasone propionate/salmeterol dry-powder inhaler; FS MDPI = fluticasone propionate/salmeterol multidose dry powder inhaler; ICS = inhaled corticosteroid; LABA = long-acting beta-agonist.*

were either mild or moderate in severity. AEs experienced by at least 3% of the subjects in any group are summarized in Table 3. SAEs occurred in 44 subjects (6.5%) at a similar incidence across the treatment groups and are summarized in Table 4. One SAE (moderate asthma, which occurred in a subject in the Fp MDPI 100 μg group) was considered by the investigator to be study drug related. No deaths occurred during the study.

Asthma exacerbations were reported by 75 subjects (11%); 26 of these were considered severe (Table 5). The incidence of asthma exacerbations was similar between the Fp MDPI and Fp HFA treatment groups as well as between the mid-strength FS MDPI and FS DPI treatment groups. However, the asthma exacerbation incidence was higher in the high-strength FS MDPI group than in the high-strength FS DPI group (15 versus 7%, respectively). Four subjects discontinued treatment due to asthma exacerbations (one in the Fp MDPI 100 μg group [moderate], two in the FS MDPI 200/12.5 μg group [one moderate, one severe], and one in the FS DPI 500/50 μg group [severe]). Among those with severe asthma exacerbations, three subjects were hospitalized but continued study treatment (one in the Fp MDPI 200 μg group and two in the FS MDPI 200/12.5 μg group). *Post hoc* analyses were conducted to determine if the incidence of asthma exacerbations was different across the treatment groups. For all comparisons, the 95% CIs included zero, which indicated that the incidences were similar based on this *post hoc* analysis.

With regard to the additional safety measures, no clinically meaningful trends were observed for any treatment group. Oral candidiasis was reported as an AE in 33 subjects during the treatment period, with higher respective incidences of 12 and 11% for the high-strength Fp HFA 440 μg and FS DPI 500/50 μg groups compared with the Fp MDPI 200 μg and FS MDPI 200/12.5 μg groups (4% incidence in both groups). No clinically meaningful changes in laboratory test results, ECGs, vital signs, or physical examinations were observed between treatment groups during the study. Urinary cortisol differences between the treatment groups within cohorts were minimal, with no apparent trends for increases or decreases in 24-hour urinary free cortisol. Three subjects in the Fp HFA group (one [2%] who received Fp HFA 220 μg b.i.d. and two [5%] who received Fp HFA 440 μg b.i.d.) had AEs of low urinary cortisol, whereas no other groups had this AE.

Efficacy

Noninferiority (demonstrated if the lower limit of the 95% CI for the treatment difference was greater than a decrease of the predefined margin of 125 mL) was

Table 1 **Subject demographics and baseline characteristics, safety population**

Characteristic	ICS Cohort				ICS/LABA Cohort			
	Mid-Strength		High-Strength		Mid-Strength		High-Strength	
	Fp MDPI 100 μg b.i.d. (*n* = 127)	Fp HFA 220 μg b.i.d. (*n* = 42)	Fp MDPI 200 μg b.i.d. (*n* = 126)*	Fp HFA 440 μg b.i.d. (*n* = 41)	FS MDPI 100/12.5 μg b.i.d. (*n* = 120)	FS DPI 250/50 μg b.i.d. (*n* = 41)	FS MDPI 200/12.5 μg b.i.d. (*n* = 133)	FS DPI 500/50 μg b.i.d. (*n* = 44)
Age, mean ± SD, y	41.5 ± 17.93	38.4 ± 18.10	42.0 ± 17.28	43.6 ± 16.74	43.9 ± 17.58	45.9 ± 17.22	46.1 ± 16.00	45.6 ± 13.92
Age group, no. (%)								
12–17 y	19 (15)	7 (17)	16 (13)	3 (7)	13 (11)	5 (12)	9 (7)	1 (2)
18–64 y	96 (76)	32 (76)	96 (76)	35 (85)	94 (78)	31 (76)	106 (80)	41 (93)
≥65 y	12 (9)	3 (7)	12 (10)	3 (7)	13 (11)	5 (12)	18 (14)	2 (5)
Sex, no. (%)								
Male	49 (39)	16 (38)	46 (37)	16 (39)	36 (30)	21 (51)	61 (46)	21 (48)
Female	78 (61)	26 (62)	78 (62)	25 (61)	84 (70)	20 (49)	72 (54)	23 (52)
Race, no. (%)								
White	110 (87)	26 (62)	99 (79)	36 (88)	99 (83)	32 (78)	95 (71)	31 (70)
Black or African American	16 (13)	13 (31)	22 (17)	5 (12)	19 (16)	9 (22)	31 (23)	12 (27)
Asian	1 (<1)	1 (2)	1 (<1)	0	2 (2)	0	4 (3)	0
Other	0	2 (5)	2 (2)	0	0	0	3 (2)	1 (2)
Missing*	0	0	2 (2)	0	0	0	0	0
BMI, mean ± SD, kg/m^2	28.6 ± 7.54	30.2 ± 7.77	29.8 ± 7.63#	30.1 ± 5.95	30.0 ± 7.85	28.9 ± 7.14	30.7 ± 7.18	32.0 ± 6.68
Former smoker, no. (%)	26 (20)	10 (24)	20 (16)	5 (12)	23 (19)	7 (17)	24 (18)	8 (18)
Baseline spirometry								
Baseline FEV_1, mean ± SD, L	2.54 ± 0.795#	2.70 ± 0.822	2.56 ± 0.847§	2.43 ± 0.792	2.54 ± 0.869	2.44 ± 0.696	2.31 ± 0.783¶	2.47 ± 0.906
Baseline FVC, mean ± SD, L	3.52 ± 1.007#	3.71 ± 1.172	3.42 ± 1.069§	3.40 ± 1.030	3.45 ± 1.107	3.48 ± 0.872	3.31 ± 1.042¶	3.40 ± 1.036
Baseline $FEF_{25–75}$, mean ± SD, L	2.11 ± 1.071#	2.34 ± 1.232	2.28 ± 1.266§	2.02 ± 1.073	2.19 ± 1.166	1.85 ± 0.927	1.91 ± 1.154¶	2.08 ± 1.397

ICS = Inhaled corticosteroid; LABA = long-acting beta-agonist; Fp = fluticasone propionate; MDPI = multidose dry powder inhaler; b.i.d. = twice daily; HFA = hydrofluoroalkane; FS = fluticasone propionate/salmeterol; DPI = dry-powder inhaler; SD = standard deviation; BMI = body mass index; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; $FEF_{25–75}$ = forced expiratory flow between 25 and 75% of the forced vital capacity.

**Two subjects from one site did not provide demographic information.*

#n = 125.

§n = 122.

¶n = 131.

Table 2 **Summary of treatment-emergent adverse events, safety population***

Subjects with at least one of the following	ICS Cohort, no. (%)				ICS/LABA Cohort, no. (%)			
	Mid-Strength		High-Strength		Mid-Strength		High-Strength	
	Fp MDPI 100 μg b.i.d. (*n* = 127)	Fp HFA 220 μg b.i.d. (*n* = 42)	Fp MDPI 200 μg b.i.d. (*n* = 125)	Fp HFA 440 μg b.i.d. (*n* = 41)	FS MDPI 100/12.5 μg b.i.d. (*n* = 120)	FS DPI 250/50 μg b.i.d. (*n* = 41)	FS MDPI 200/12.5 μg b.i.d. (*n* = 133)	FS DPI 500/50 μg b.i.d. (*n* = 44)
TEAE	85 (67)	29 (69)	83 (66)	29 (71)	92 (77)	29 (71)	86 (65)	30 (68)
Treatment-related TEAE	10 (8)	2 (5)	6 (5)	5 (12)	9 (8)	4 (10)	11 (8)	8 (18)
Serious TEAE	7 (6)	2 (5)	8 (6)	3 (7)	6 (5)	2 (5)	13 (10)	3 (7)
TEAE that led to withdrawal	2 (2)	1 (2)	0	1 (2)	3 (3)	2 (5)	0	1 (2)

ICS = Inhaled corticosteroid; LABA = long-acting beta-agonist; Fp = fluticasone propionate; MDPI = multidose dry powder inhaler; b.i.d. = twice daily; HFA = hydrofluoroalkane; FS = fluticasone propionate/salmeterol; DPI = dry-powder inhaler; TEAE = treatment-emergent adverse event.

**The subjects were counted only once in each category.*

established for all Fp MDPI and FS MDPI doses compared with Fp HFA and FS DPI doses, respectively, for FEV_1 (Fig. 2). All pulmonary function variables (FEV_1, FVC, and $FEF_{25–75}$) were comparable between the Fp MDPI and Fp HFA treatment groups and between the FS MDPI and FS DPI treatment groups (Table 6). Sixty-three subjects used rescue medication over the 26-week treatment period (Table 6). The proportion of subjects who used rescue medication was similar among the Fp MDPI and FS MDPI treatment groups and their respective comparator treatment groups (Table 6). The subjects within the ICS and ICS/LABA groups experienced similar increases in A.M. PEF when treated with Fp MDPI, Fp HFA, FS MDPI, and FS DPI (Table 6). Changes from baseline in the asthma symptom scores were similar between the Fp MDPI groups and comparator Fp HFA groups and between the FS MDPI groups and comparator FS DPI groups (Table 6). Four subjects withdrew from the study due to worsening asthma symptoms during the 26-week treatment period (one subject in the Fp MDPI 100 μg group, two in the FS MDPI 200/12.5 μg group, and one in the FS DPI 500/50 μg group).

DISCUSSION

In this open-label study, treatment with Fp MDPI or FS MDPI for up to 26 weeks was safe and well tolerated in subjects with persistent asthma. The incidence of TEAEs, SAEs, and AEs was similar between the treatment groups. The types of AEs reported in the current study were consistent with those previously reported in earlier Fp and FS clinical studies and with the classes of drugs and underlying disease.[13,14,19–21] Reported TEAEs, SAEs, and AEs that necessitated study withdrawal were rare and similar between the treatment groups. There were no notable differences in laboratory results, ECGs, vital signs, physical examination, or urinary cortisol results between the Fp MDPI and FS MDPI groups and between the Fp HFA and FS DPI groups. As would be expected, higher incidences of candidiasis and/or low urinary cortisol results were observed in the high-strength Fp HFA and FS DPI groups, which indicated greater topical or systemic corticosteroid effects. The data available on the effects of ICS on ocular safety are minimal and conflicting.[22] In the present 6-month study, there were no incidences of glaucoma or cataracts in any subject who received an Fp or FS combination.

The effect of Fp DPI on growth rate in children has been studied in several long- and short-term studies.[23–25] The overall conclusion has been that Fp DPI has a positive risk-to-benefit profile and children treated for 1 year grew at similar rates compared with children treated with placebo.[23–25] Growth was not evaluated in the present study because the majority of the subjects were ≥18 years of age, with only 12%

Table 3 **Incidence of treatment-emergent adverse events reported by at least 3% of subjects, safety population**

MedDRA v17.0 Preferred Term	ICS Cohort, no. (%)				ICS/LABA Cohort, no. (%)			
	Mid-Strength		High-Strength		Mid-Strength		High-Strength	
	Fp MDPI 100 μg b.i.d. (*n* = 127)	Fp HFA 220 μg b.i.d. (*n* = 42)	Fp MDPI 200 μg b.i.d. (*n* = 125)	Fp HFA 440 μg b.i.d. (*n* = 41)	FS MDPI 100/12.5 μg b.i.d. (*n* = 120)	FS DPI 250/50 μg b.i.d. (*n* = 41)	FS MDPI 200/12.5 μg b.i.d. (*n* = 133)	FS DPI 500/50 μg b.i.d. (*n* = 44)
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
Pyrexia	3 (2)	1 (2)	3 (2)	0	3 (3)	0	3 (2)	3 (7)
Upper respiratory tract infection	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)
Procedural pain	1 (<1)	0	1 (<1)	2 (5)	1 (<1)	2 (5)	1 (<1)	0
Cortisol free urine decreased	0	1 (2)	0	2 (5)	0	0	0	0
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
Headache	5 (4)	2 (5)	6 (5)	1 (2)	9 (8)	4 (10)	3 (2)	2 (5)
Asthma	6 (5)	0	4 (3)	0	3 (3)	1 (2)	9 (7)	2 (5)
Oropharyngeal pain	13 (10)	5 (12)	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)

MedDRA = Medical Dictionary for Regulatory Activities; ICS = inhaled corticosteroid; LABA = long-acting beta-agonist; Fp = fluticasone propionate; MDPI = multidose dry powder inhaler; b.i.d. = twice daily; HFA = hydrofluoroalkane; FS = fluticasone propionate/salmeterol; DPI = dry-powder inhaler.

Table 4 **Incidence of serious treatment-emergent adverse events with one or more events in at least one treatment group, safety population**

MedDRA v17.0 Preferred Term	ICS Cohort, no. (%)				ICS/LABA Cohort, no. (%)			
	Mid-Strength		High-Strength		Mid-Strength		High-Strength	
	Fp MDPI 100 μg b.i.d. (*n* = 127)	Fp HFA 220 μg b.i.d. (*n* = 42)	Fp MDPI 200 μg b.i.d. (*n* = 125)	Fp HFA 440 μg b.i.d. (*n* = 41)	FS MDPI 100/12.5 μg b.i.d. (*n* = 120)	FS DPI 250/50 μg b.i.d. (*n* = 41)	FS MDPI 200/12.5 μg b.i.d. (*n* = 133)	FS DPI 500/50 μg b.i.d. (*n* = 44)
Subjects with ≥1 serious TEAE	7 (6)	2 (5)	8 (6)	3 (7)	6 (5)	2 (5)	13 (10)	3 (7)
Acute myocardial infarction	0	0	1 (<1)	0	0	0	0	0
Atrial tachycardia	0	0	0	1 (2)	0	0	0	0
Device dislocation	0	0	0	1 (2)	0	0	0	0
Noncardiac chest pain	0	0	0	0	1 (<1)	0	0	0
Biliary colic	1 (<1)	0	0	0	0	0	1 (<1)	0
Cholelithiasis	1 (<1)	0	0	0	0	0	0	0
Bronchitis	0	0	0	0	0	0	1 <1)	0
Pneumonia	0	0	0	0	0	0	1 (<1)	1 (2)
Cellulitis	0	0	0	1 (2)	0	0	0	0
Lobar pneumonia	0	0	1 (<1)	0	0	0	0	0
Humerus fracture	0	0	0	0	0	0	1 (<1)	0
Procedural pain	0	0	0	0	0	0	1 (<1)	0
Fall	0	1 (2)	0	0	0	0	0	0
Hip fracture	0	1 (2)	0	0	0	0	0	0
Wound dehiscence	0	0	0	1 (2)	0	0	0	0
Basal cell carcinoma	0	0	0	0	0	0	1 (<1)	0
Leiomyoma	0	0	0	0	1 (<1)	0	0	0
Malignant melanoma	0	0	0	0	0	1 (2)	0	0
Non–small cell lung cancer	0	0	0	0	1 (<1)	0	0	0
Uterine leiomyoma	0	0	0	0	1 (<1)	0	0	0
Abortion spontaneous	0	0	1 (<1)	0	0	0	0	0

Table 4 **Continued**

MedDRA v17.0 Preferred Term	ICS Cohort, no. (%)				ICS/LABA Cohort, no. (%)			
	Mid-Strength		High-Strength		Mid-Strength		High-Strength	
	Fp MDPI 100 μg b.i.d. (*n* = 127)	Fp HFA 220 μg b.i.d. (*n* = 42)	Fp MDPI 200 μg b.i.d. (*n* = 125)	Fp HFA 440 μg b.i.d. (*n* = 41)	FS MDPI 100/12.5 μg b.i.d. (*n* = 120)	FS DPI 250/50 μg b.i.d. (*n* = 41)	FS MDPI 200/12.5 μg b.i.d. (*n* = 133)	FS DPI 500/50 μg b.i.d. (*n* = 44)
Ectopic pregnancy	0	0	1 (<1)	0	0	0	0	0
Asthma	6 (5)	0	4 (3)	0	3 (3)	1 (2)	8 (6)	2 (5)
Pulmonary embolism	0	1 (2)	0	0	0	0	0	0
Pulmonary mass	0	0	1 (<1)	0	0	0	0	0

MedDRA = Medical Dictionary for Regulatory Activities; ICS = inhaled corticosteroid; LABA = long-acting beta-agonist; Fp = fluticasone propionate; MDPI = multidose dry powder inhaler; b.i.d. = twice daily; HFA = hydrofluoroalkane; FS = fluticasone propionate/salmeterol; DPI = dry-powder inhaler: TEAE = treatment-emergent adverse event.

Table 5 **Incidence of asthma exacerbation, safety population**

	ICS Cohort, no. (%)				ICS/LABA Cohort, no. (%)			
	Mid-Strength		High-Strength		Mid-Strength		High-Strength	
	Fp MDPI 100 μg b.i.d. (*n* = 127)	Fp HFA 220 μg b.i.d. (*n* = 42)	Fp MDPI 200 μg b.i.d. (*n* = 125)	Fp HFA 440 μg b.i.d. (*n* = 41)	FS MDPI 100/12.5 μg b.i.d. (*n* = 120)	FS DPI 250/50 μg b.i.d. (*n* = 41)	FS MDPI 200/12.5 μg b.i.d. (*n* = 133)	FS DPI 500/50 μg b.i.d. (*n* = 44)
Subjects with at least 1 asthma exacerbation	13 (10)	5 (12)	13 (10)	3 (7)	13 (11)	5 (12)	20 (15)	3 (7)
Severity								
Mild	1 (<1)	2 (5)	3 (2)	1 (2)	2 (2)	2 (5)	5 (4)	0
Moderate	5 (4)	3 (7)	5 (4)	1 (2)	8 (7)	3 (7)	7 (5)	1 (2)
Severe	7 (6)	0	5 (4)	1 (2)	3 (3)	0	8 (6)	2 (5)

ICS = Inhaled corticosteroid; LABA = long-acting beta-agonist; Fp = fluticasone propionate; MDPI = multidose dry powder inhaler; b.i.d. = twice daily; HFA = hydrofluoroalkane; FS = fluticasone propionate/salmeterol; DPI = dry-powder inhaler.

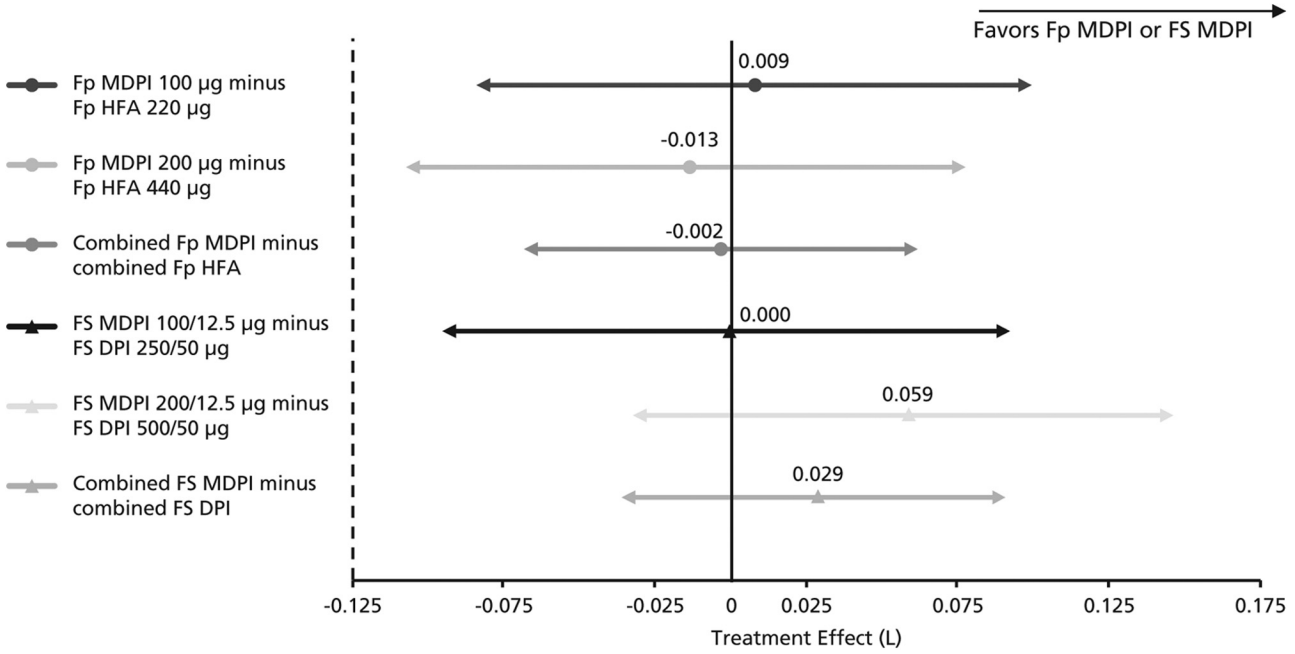

Figure 2. *Trough FEV_1 (L) treatment effect analysis for noninferiority, full analysis set; noninferiority was specified as the lower limit of the two-sided 95% CI for the treatment difference being greater than −0.125 L. FEV_1 = Forced expiratory volume in 1 second; CI = confidence interval; Fp HFA = fluticasone propionate hydrofluoroalkane; Fp MDPI = fluticasone propionate multidose dry powder inhaler; FS DPI = fluticasone propionate/salmeterol dry-powder inhaler; FS MDPI = fluticasone propionate/salmeterol multidose dry powder inhaler.*

within the age range eligible for growth studies. Some of the study groups contained as few as one, three, or five subjects in the 12- to 17-year age group. However, a review of the data indicated that, overall, there was no effect on growth in subjects 12 to 17 years of age treated with Fp MDPI or FS MDPI.

Noninferiority in efficacy was demonstrated for all doses of Fp MDPI and FS MDPI despite use of much lower doses of Fp and salmeterol compared with doses of Fp HFA and FS DPI, respectively. Improvements in pulmonary function were maintained over the 26 weeks of treatment, with no evidence of a diminution of effect. Similar changes were observed for other measures of pulmonary function ($FEF_{25–75}$ and FVC) and efficacy (PEF, symptoms, and rescue albuterol use) between the Fp and FS MDPI groups relative to the Fp HFA and FS DPI groups, which indicated that Fp and FS MDPI provided similar clinical benefits to those of Fp HFA or FS DPI, despite use of lower doses.

The incidence of asthma exacerbations was low and generally similar among the various treatment groups. Although small differences between the treatment groups were observed for some of the comparisons, these were likely due to chance caused by the 3:1 randomization and resultant small number of subjects in the comparator groups and rarity of events. The *post hoc* statistical analysis confirmed that these small differences were unlikely to be treatment related. This open-label safety study was not designed to evaluate treatment differences in the incidence of asthma exacerbations. As such, a history of asthma exacerbations was not collected, and, therefore, a balance in randomization could not be confirmed across the treatment groups.

The MDPI device was designed to improve the pulmonary delivery of Fp and salmeterol such that lower doses could achieve similar clinical benefits to those seen with the much higher doses of the Fp HFA and FS DPI products. The evidence that greater pulmonary delivery of inhaled therapies can be associated with comparable clinical efficacy at lower doses is supported by the development of beclomethasone dipropionate HFA, in which lower doses of beclomethasone HFA that result in higher lung deposition were able to provide comparable benefits to higher doses of the chlorofluorocarbon propellant formulation.[26] Indeed, two dose-ranging studies, one with Fp MDPI and the other with FS MDPI, confirmed that the lower doses of Fp and salmeterol in the MDPI device can provide similar benefits to Fp HFA or FS DPI with similar or less systemic exposure.[15,16] In both studies, evidence of a dose response was observed with Fp MDPI and FS MDPI, which demonstrates assay sensitivity and the ability to discriminate doses in the trials.[15,16]

Due to the difficulty in blinding the active comparator treatments, an open-label study design had to be used for this safety and efficacy trial, which may limit the conclusiveness of the comparisons within and across the treatment groups. The randomized study design, inclusion of subjects with varying baseline asthma severity, and treatment stratification commensurate with the subjects'

Table 6 **Efficacy of mid- and high-strength Fp MDPI, FS MDPI, and comparator therapies, full analysis set**

Variable Statistic	ICS Cohort				ICS/LABA Cohort			
	Mid-Strength		High-Strength		Mid-Strength		High-Strength	
	Fp MDPI 100 μg b.i.d. (n = 123)	Fp HFA 220 μg b.i.d. (n = 42)	Fp MDPI 200 μg b.i.d. (n = 120)	Fp HFA 440 μg b.i.d. (n = 41)	FS MDPI 100/12.5 μg b.i.d. (n = 119)	FS DPI 250/50 μg b.i.d. (n = 40)	FS MDPI 200/12.5 μg b.i.d. (n = 130)	FS DPI 500/50 μg b.i.d. (n = 44)
Change from baseline in trough FEV_1, L								
LS mean ± SE	0.062 ± 0.0243	0.053 ± 0.0415	0.077 ± 0.0246	0.090 ± 0.0415	0.116 ± 0.0251	0.117 ± 0.0419	0.100 ± 0.0235	0.041 ± 0.0399
95% CI of the comparison of Fp MDPI vs Fp HFA and FS MDPI vs FS DPI	−0.084 to 0.103		−0.107 to 0.081		−0.095 to 0.095		−0.032 to 0.150	
Change from baseline in FVC, L								
LS mean ± SE	0.058 ± 0.0252	0.036 ± 0.0434	0.071 ± 0.0255	0.044 ± 0.0437	0.082 ± 0.0256	0.094 ± 0.0441	0.041 ± 0.0247	0.042 ± 0.0421
95% CI of the comparison of Fp MDPI vs Fp HFA and FS MDPI vs FS DPI	−0.076 to 0.121		−0.073 to 0.126		−0.112 to 0.089		−0.097 to 0.095	
Change from baseline in FEF_{25-75}, L								
LS mean ± SE	0.075 ± 0.0418	0.059 ± 0.0721	0.072 ± 0.0424	0.079 ± 0.0724	0.080 ± 0.0425	0.083 ± 0.0733	0.134 ± 0.0410	0.082 ± 0.0699
95% CI of the comparison of Fp MDPI vs Fp HFA and FS MDPI vs FS DPI	−0.147 to 0.180		−0.171 to 0.158		−0.170 to 0.163		−0.106 to 0.212	
Change from baseline in A.M. PEF, L/min*								
LS mean ± SE	6.860 ± 2.761	0.741 ± 4.786	7.315 ± 2.816	5.349 ± 4.783	1.596 ± 2.807	3.354 ± 4.839	5.789 ± 2.700	7.738 ± 4.662
95% CI of the comparison of Fp MDPI vs Fp HFA and FS MDPI vs FS DPI	−4.734 to 16.973		−8.933 to 12.865		−12.734 to 9.217		−12.535 to 8.638	
Rescue medication used during the 26-week treatment period for worsening asthma								
No. subjects	13	3	10	3	10	5	16	3
No. puffs, mean ± SD	31 ± 31.8	44 ± 24.0	49 ± 39.5	21 ± 25.7	30 ± 31.7	10 ± 10.6	36 ± 47.2	55 ± 61.5

Table 6 **Continued**

Variable Statistic	ICS Cohort				ICS/LABA Cohort			
	Mid-Strength		High-Strength		Mid-Strength		High-Strength	
	Fp MDPI 100 μg b.i.d. (*n* = 123)	**Fp HFA 220 μg b.i.d. (*n* = 42)**	**Fp MDPI 200 μg b.i.d. (*n* = 120)**	**Fp HFA 440 μg b.i.d. (*n* = 41)**	**FS MDPI 100/12.5 μg b.i.d. (*n* = 119)**	**FS DPI 250/50 μg b.i.d. (*n* = 40)**	**FS MDPI 200/12.5 μg b.i.d. (*n* = 130)**	**FS DPI 500/50 μg b.i.d. (*n* = 44)**
Change from baseline in weekly average of the total daily asthma symptom scores#								
LS mean ± SE	−0.077 ± 0.0271	−0.072 ± 0.0468	−0.155 ± 0.0275	−0.139 ± 0.0468	−0.088 ± 0.0275	−0.132 ± 0.0473	−0.111 ± 0.0263	−0.107 ± 0.0450
95% CI of the comparison of Fp MDPI versus Fp HFA and FS MDPI versus FS DPI	−0.111 to 0.101		−0.123 to 0.090		−0.063 to 0.152		−0.106 to 0.098	

Fp = Fluticasone propionate; MDPI = multidose dry powder inhaler; FS = fluticasone propionate/salmeterol; ICS = inhaled corticosteroid; LABA = long-acting beta-agonist; b.i.d. = twice daily; DPI = dry powder inhaler; FEV_1 = forced expiratory volume in 1 second; LS = least square; SE = standard error; CI = confidence interval; FVC = forced vital capacity; $FEF_{25–75}$ = forced expiratory flow between 25 and 75% of the forced vital capacity; PEF = peak expiratory flow; SD = standard deviation.

**n = 41 for Fp HFA 220 μg, n = 118 for Fp MDPI 200 μg, n = 129 for FS MDPI 200/12.5 μg, and n = 43 for FS DPI 500/50 μg.*

#n = 41 for Fp HFA 220 μg, n = 118 for Fp MDPI 200 μg, and n = 129 for FS MDPI 200/12.5 μg.

asthma severity provide reassurance that the safety and efficacy comparisons are likely to reflect the safety and effectiveness of these agents when used in a real-world setting. In addition, the efficacy and safety results were consistent with what has been observed with Fp HFA and FS DPI in other similar clinical trials,[27–30] which indicats that the safety and efficacy results and conclusions are unlikely to be influenced by the use of an open-label design.

CONCLUSION

In this phase III, randomized, open-label study, treatment with Fp MDPI and FS MDPI for up to 26 weeks demonstrated safety and efficacy profiles that were comparable with those of Fp HFA and FS DPI, respectively, in subjects with persistent asthma, despite the use of lower doses of Fp and salmeterol.

REFERENCES

1. Expert Panel Report 3 (EPR3): Guidelines for the Diagnosis and Management of Asthma. Bethesda, MD: National Heart, Lung, and Blood Institute, US Department of Health and Human Services, 2007.
2. Stempel DA, Raphiou IH, Kral KM, et al. Serious asthma events with fluticasone plus salmeterol versus fluticasone alone. N Engl J Med 374:1822–1830, 2016.
3. Nelson HS, Weiss ST, Bleecker ER, et al. The Salmeterol Multicenter Asthma Research Trial: A comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 129:15–26, 2006.
4. Castle W, Fuller R, Hall J, and Palmer J. Serevent nationwide surveillance study: Comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. BMJ 306:1034–1037, 1993.
5. Mann M, Chowdhury B, Sullivan E, et al. Serious asthma exacerbations in asthmatics treated with high-dose formoterol. Chest 124:70–74, 2003.
6. Weatherall M, Wijesinghe M, Perrin K, et al. Meta-analysis of the risk of mortality with salmeterol and the effect of concomitant inhaled corticosteroid therapy. Thorax 65:39–43, 2010.
7. Price DB, Pearce L, Powell SR, et al. Handling and acceptability of the Easi-Breathe device compared with a conventional metered dose inhaler by patients and practice nurses. Int J Clin Pract 53:31–36, 1999.
8. Brocklebank D, Ram F, Wright J, et al. Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: A systematic review of the literature. Health Technol Assess 5:1–149, 2001.
9. Giraud V, and Roche N. Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability. Eur Respir J 19:246–251, 2002.
10. Virchow JC, Crompton GK, Dal Negro R, et al. Importance of inhaler devices in the management of airway disease. Respir Med 102:10–19, 2008.
11. O'Conor R, Wolf MS, Smith SG, et al. Health literacy, cognitive function, proper use and adherence to inhaled asthma controller medications among older adults with asthma. Chest 147: 1307–1315, 2015.
12. Vutikullird AB, Gillespie M, Song S, and Steinfeld J. Pharmacokinetics, safety, and tolerability of a new fluticasone propionate multidose dry powder inhaler compared with fluticasone propionate Diskus® in healthy adults. J Aerosol Med Pulm Drug Deliv 29:207–214, 2016.
13. Flovent HFA [package insert]. Research Triangle Park, NC: GlaxoSmithKline, 2014.
14. Advair Diskus [package insert]. Research Triangle Park, NC: GlaxoSmithKline, 2014.
15. Kerwin EM, Gillespie M, Song S, and Steinfeld J. Randomized, dose-ranging study of a fluticasone propionate multidose dry powder inhaler in adolescents and adults with uncontrolled asthma not previously treated with inhaled corticosteroids. J Asthma 54:89–98, 2017.
16. Miller DS, Yiu G, Hellriegel ET, and Steinfeld J. Dose-ranging study of salmeterol using a novel fluticasone propionate/salmeterol multidose dry powder inhaler in patients with persistent asthma. Allergy Asthma Proc 37:291–301, 2016.
17. Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994. U.S. Department of Health & Human Services. Atlanta, GA. Available at: https://www.cdc.gov/nchs/nhanes/nhanes3.htm.
18. Santanello NC, Zhang J, Seidenberg B, et al. What are minimal important changes for asthma measures in a clinical trial? Eur Respir J 14:23–27, 1999.
19. Bateman ED, Boushey HA, Bousquet J, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. Am J Respir Crit Care Med 170:836–844, 2004.
20. Lasserson TJ, Ferrara G, and Casali L. Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children. Cochrane Database Syst Rev 2011(12):CD004106.
21. Flovent Diskus [package insert]. Research Triangle Park, NC: GlaxoSmithKline, 2014.
22. Carr WW, and Szefler SJ. Inhaled corticosteroids: Ocular safety and the hypothalamic-pituitary-adrenal axis. Ann Allergy Asthma Immunol 117:589–594, 2016.
23. Visser MJ, van Aalderen WM, Elliott BM, et al. Short-term growth in asthmatic children using fluticasone propionate. Chest 113:584–586, 1998.
24. de Benedictis FM, Teper A, Green RJ, et al. Effects of 2 inhaled corticosteroids on growth: Results of a randomized controlled trial. Arch Pediatr Adolesc Med 155:1248–1254, 2001.
25. Allen DB, Bronsky EA, LaForce CF, et al. Growth in asthmatic children treated with fluticasone propionate. Fluticasone Propionate Asthma Study Group. J Pediatr 132:472–477, 1998.
26. Busse WW, Brazinsky S, Jacobson K, et al. Efficacy response of inhaled beclomethasone dipropionate in asthma is proportional to dose and is improved by formulation with a new propellant. J Allergy Clin Immunol 104:1215–1222, 1999.
27. Kavuru M, Melamed J, Gross G, et al. Salmeterol and fluticasone propionate combined in a new powder inhalation device for the treatment of asthma: A randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunol 105:1108–1116, 2000.
28. Bateman ED, Silins V, and Bogolubov M. Clinical equivalence of salmeterol/fluticasone propionate in combination (50/100 microg twice daily) when administered via a chlorofluorocarbon-free metered dose inhaler or dry powder inhaler to patients with mild-to-moderate asthma. Respir Med 95:136–146, 2001.
29. Ayres JG, Millar AB, and Sykes AP. Clinical efficacy and safety of fluticasone propionate 1 mg twice daily administered via a HFA 134a pressurized metered dose inhaler to patients with severe asthma. U.K. study group. Respir Med 94(suppl. B):S42–S50, 2000.
30. Perruchoud AP, Lundback B, Yigla M, and Sykes AP. Clinical efficacy and safety of fluticasone propionate 1 mg per day administered via a HFA 134a pressurized metered dose inhaler to patients with moderate to severe asthma. International study group. Respir Med 94(suppl. B):S35–S41, 2000. □