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PHARMACOTHERAPY

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

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ABSTRACT

Objective: A novel, inhalation-driven, multidose dry powder inhaler (MDPI) eliminates the need to coordinate actuation with inhalation. To characterize dose response, efficacy, and safety of fluticasone propionate (Fp) MDPI, a dose-ranging study was conducted with placebo and active comparators. **Methods:** This 12-week, double-blind, parallel-group study randomized patients aged ≥ 12 years with uncontrolled persistent asthma not previously treated with inhaled corticosteroid therapy ($N = 622$) to twice-daily treatment with Fp MDPI (12.5, 25, 50, or 100 μg), placebo MDPI, or open-label Fp dry powder inhaler (DPI) 100 μg . The primary efficacy endpoint was change from baseline over 12 weeks in trough (morning pre-dose and pre-rescue bronchodilator) forced expiratory volume in 1 second (FEV_1). Blood samples were collected from a patient subset to evaluate pharmacokinetics. Adverse events were monitored. **Results:** Fp MDPI 25, 50, and 100 μg significantly improved change from baseline in trough FEV_1 over 12 weeks compared with placebo ($p < 0.01$). There were no substantial differences in FEV_1 change from baseline over 12 weeks between any Fp MDPI dose and Fp DPI 100 μg . Maximum observed concentration (C_{max}) of Fp increased with increasing Fp MDPI doses; time of C_{max} was similar across doses and treatments. Systemic exposures for Fp MDPI 25 and 50 μg were lower than that for Fp DPI 100 μg . The safety profile of Fp MDPI was consistent with that of Fp DPI. **Conclusions:** In this study, Fp MDPI 25 and 50 μg provided comparable efficacy and safety to Fp DPI 100 μg , with lower systemic exposure.

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Introduction

Airway inflammation leads to the signs and symptoms of asthma, including airway hyperresponsiveness and airflow limitation [1]. The underlying inflammatory response is central to the pathophysiology of asthma and the basis for treatment guidelines that currently recommend the use of daily long-term anti-inflammatory control medications, with inhaled corticosteroids (ICSs) identified as the most potent and consistently effective treatment [1]. In addition to long-term ICS, quick-relief medications (inhaled short-acting β_2 -adrenergic agonists [SABAs]) are recommended to relieve symptoms, as needed, in patients with persistent asthma [1].

Fluticasone propionate (Fp) is an ICS approved for the maintenance treatment of asthma in patients ≥ 4 years of age [2]. Initially approved by the US Food and Drug Administration in 1994, Fp has a well-established safety and efficacy profile with benefits observed for all levels of persistent asthma severity. Fluticasone propionate is currently marketed as a metered dose inhaler (MDI)

in doses of 220, 110, and 44 μg , and as a dry powder inhaler (DPI; Flovent[®] Diskus[®]; GlaxoSmithKline, Research Triangle Park, NC) available in strengths of 50, 100, and 250 μg . Flovent Diskus (100 μg) twice-daily inhaler was utilized as the active control medication for this study, designated as Fp DPI.

Good inhaler technique is an important aspect of asthma control [3]. The inability to coordinate manual actuation with inhalation may compromise drug delivery to the airways, potentially resulting in suboptimal efficacy [4]. A novel, inhalation-driven, multidose dry powder inhaler (MDPI; Teva Pharmaceuticals, Inc., Frazer, PA; device is currently marketed in the United States to deliver albuterol [ProAir[®] RespiClick]) has been developed that eliminates the need for patients to coordinate device actuation with inhalation for the delivery of either inhaled controller or rescue asthma medication. The characteristics of the MDPI provide patients with an asthma management approach that can deliver rescue or maintenance medication individually and can utilize the same delivery device for multiple medications.

A recent prospective, open-label study evaluated the MDPI with an integrated dose counter in 317 patients ≥ 4 years of age with asthma or chronic obstructive pulmonary disease. This open-label study demonstrated that 83% of the patients reported being somewhat-to-very satisfied with the inhaler with the integrated dose counter, 92% were satisfied with the ease of holding and handling the inhaler, and 85% were satisfied with the ease of learning to use the inhaler [5].

The efficacy, pharmacokinetic, and pharmacodynamic profiles of albuterol delivered via the MDPI has been demonstrated to be comparable with those of albuterol hydrofluoroalkane (HFA) MDI in 2 double-blind, randomized, double-dummy, crossover, placebo-controlled studies in patients with persistent asthma [6]. In addition, in healthy subjects, single-dose administration of Fp via the MDPI produced systemic exposure comparable with Fp DPI at lower inhaled doses and was generally well tolerated in healthy adults [7,8].

The objective of the current study was to characterize the dose response, efficacy, pharmacokinetics, and safety of Fp MDPI at 4 dose strengths in patients with uncontrolled asthma not previously treated with inhaled corticosteroid therapy. Placebo MDPI and Fp DPI 100 μg values were included for comparison.

Methods

Study design

This was a randomized, double-blind, placebo- and open-label, active-controlled, parallel-group, multicenter, dose-ranging study in patients aged ≥ 12 years with uncontrolled asthma not previously treated with inhaled corticosteroid therapy (ClinicalTrials.gov identifier: NCT01479621). The study was conducted in clinical

sites across the United States, Bulgaria, Croatia, Hungary, Israel, Poland, Serbia, Spain, and Ukraine. During the screening period, patients continued using their current asthma medications (noncorticosteroid maintenance medication and SABA rescue medication) and were instructed to administer 1 inhalation of placebo MDPI twice daily in a single-blind manner (Figure 1). At the end of the run-in period, patients discontinued all current maintenance medications and were randomized to 1 of 6 treatment groups in a 1:1:1:1:1:1 ratio using a stratified permuted block randomization procedure with pharmacokinetic (PK) cohort participation as the stratification variable: 1) placebo MDPI twice daily; 2) Fp MDPI 12.5 μg $\times$ 1 inhalation twice daily (25 μg total daily dose); 3) Fp MDPI 25 μg $\times$ 1 inhalation twice daily (50 μg total daily dose); 4) Fp MDPI 50 μg $\times$ 1 inhalation twice daily (100 μg total daily dose); 5) Fp MDPI 100 μg $\times$ 1 inhalation twice daily (200 μg total daily dose); and 6) Fp DPI (Flovent[®] Diskus[®]; Glaxo-SmithKline, Research Triangle Park, NC) 100 μg $\times$ 1 inhalation twice daily (200 μg total daily dose). Placebo and Fp MDPI devices were identical in appearance, and both investigators and patients were blinded to treatment randomization. Fluticasone propionate DPI was administered in an open-label manner. The treatment period was 12 weeks in duration, with clinic visits at weeks 1, 2, 4, 8, and 12, and a follow-up visit 1 week after week 12. Albuterol/salbutamol HFA MDI was provided to all patients as rescue medication to be used as needed for relief of asthma symptoms.

The study was approved by an independent Ethics Committee or Institutional Review Board and conducted in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6). Written informed consent was obtained from each patient prior to study procedures

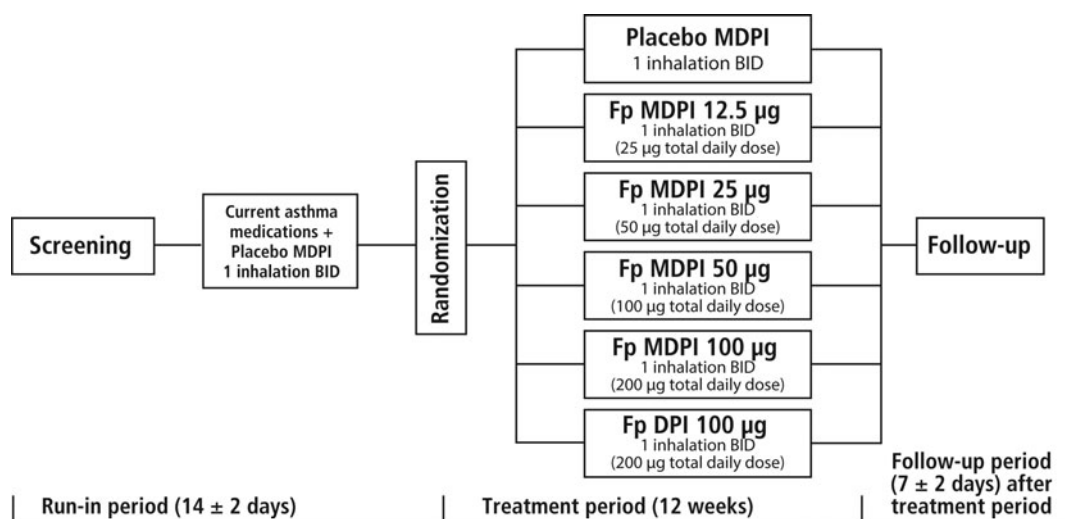


Figure 1. Study design. BID, twice daily; DPI, dry powder inhaler; Fp, fluticasone propionate; MDPI, multidose dry powder inhaler.

or assessments. The study was conducted and monitored by Pharmaceutical Product Development (PPD), Morrisville, NC.

Patients

Male or female patients with a diagnosis of persistent asthma were included if they were aged ≥ 12 years and had a best forced expiratory volume in 1 second (FEV₁) of 40%–85% of the predicted normal value. Airway reversibility, as demonstrated by a $\geq 15\%$ increase in FEV₁ within 30 minutes after 2–4 inhalations of albuterol/salbutamol (90 μg /actuation), was also required for study inclusion[9]. The following prior asthma therapies were allowed: SABAs alone, non-corticosteroid maintenance therapy (continued through screening and discontinued at randomization), and low-dose ICS (100 μg fluticasone propionate twice daily or therapeutic equivalent) as long as it was discontinued ≥ 2 weeks before screening. The combination of ICS/long-acting β_2 -adrenergic agonists was prohibited within 6 weeks of screening for this study.

Patients were excluded if they had a history of life-threatening asthma, respiratory infection within 2 weeks of screening, any asthma exacerbation requiring oral corticosteroids or change in or addition of asthma medication within 3 months, or hospitalization for asthma within 6 months of screening. Other exclusion criteria included a history of clinically significant disease, use of immunosuppressive medications within 4 weeks of screening, use of tobacco products within the past year, or smoking history of 10 pack-years or more. Female patients could not be pregnant, breastfeeding, or attempting to become pregnant; they also had to have a negative serum pregnancy test, be of nonchildbearing potential, or be willing to commit to using a consistent and acceptable method of birth control for the duration of the study.

Patients were randomized to the study if they met inclusion criteria for FEV₁ and airway reversibility and had symptom scores (≥ 1 daytime plus nighttime) or albuterol/salbutamol use on at least 4 of the last 7 consecutive days of the run-in period. Patients also had to demonstrate compliance through completion of the daily diary for symptom scores, rescue medication use, peak expiratory flow (PEF) measurements, and medication use on at least 4 of the final 7 run-in days.

Assessments

The primary efficacy endpoint was the change from baseline in trough (morning pre-dose and pre-rescue bronchodilator) FEV₁ over the 12-week treatment period. Pulmonary function tests were conducted at weeks 1, 2,

4, 8, and 12 before administration of the morning dose of study drug and before albuterol/salbutamol administration. Secondary efficacy endpoints included change from baseline in weekly average of daily trough morning and evening PEF and change from baseline in percentages of rescue-free 24-hour periods during the 12 weeks of treatment, and time to withdrawal due to meeting stopping criteria for worsening asthma.

Change from baseline in the Asthma Control Test (ACT) and change from baseline in percentages of symptom-free 24-hour periods during the 12 weeks of treatment also were evaluated. Stopping criteria were met if a patient had clinic FEV₁ below the FEV₁ stability limit, a clinical asthma exacerbation, or any of the following during any 7-day window: >3 days in which PEF fell below the PEF stability limit or >2 days using ≥ 12 inhalations of albuterol/salbutamol per day. The FEV₁ stability limit was calculated for each patient at treatment visit 1 by multiplying the best pre-albuterol/salbutamol FEV₁ at treatment visit 1 by 80%. The PEF stability limit was calculated for each patient at treatment visit 1 by multiplying the mean morning PEF from the 7 days before treatment visit 1 by 80%.

In a subset of patients randomized to Fp MDPI or Fp DPI, blood samples for determining Fp plasma concentrations (Xenobiotics Laboratories, Plainsboro, NJ) were obtained pre-dose (within 10 minutes before dose administration) and post-dose at 5, 10, 15, 30, 45, 60, 75, and 90 minutes and 2, 4, 8, and 12 hours. Evaluated PK parameters included area under the plasma concentration-vs-time curve from time zero to the time of the last quantifiable concentration (AUC_{0-t}), maximum observed plasma concentration (C_{max}), and time of maximum observed plasma concentration (t_{max}).

Safety was assessed by evaluating reported adverse events (AEs), laboratory test results, vital signs measurements, electrocardiogram findings, oropharyngeal examination findings, physical examination findings, and concomitant medication usage.

Statistical analyses

Sample size and power calculations were based on the linear in log-dose time-averaged trend test and on the comparison between the highest Fp MDPI dose (100 μg twice daily) and placebo, using a repeated measures mixed model with fixed effects of treatment, visit and treatment-by-visit interaction. (For simplicity, a compound symmetry covariance structure was assumed for the repeated observations within a patient.) A simulation study with 2000 runs was carried out to investigate the sample size requirement.

Assuming a true time-averaged (i.e., averaged over 12 weeks) treatment difference of 200 mL between the highest Fp MDPI dose (100 µg twice daily) and placebo, a common standard deviation of 450 mL, 5 repeated post-baseline measurements of trough FEV₁ for each patient, and a correlation coefficient of 0.7 among repeated observations within a patient, 85 patients per treatment group (a total of 510 patients) would provide a statistical power of ~90%, at the 2-sided 0.05 level of significance, to detect a linear in log-dose time-averaged trend and for identifying at least 1 Fp MDPI dose that is effective. Assuming a drop-out rate of about 15%, approximately 100 patients per treatment group (a total of 600 patients) were randomized in this study to ensure that a minimum of approximately 510 patients completed all visits and critical assessments.

Efficacy analyses were completed for the full analysis set (FAS), which included all patients in the intent-to-treat population (all randomized patients), who received at least 1 dose of study drug and had at least 1 post-baseline trough FEV₁ assessment. The intent-to-treat (ITT) population, which included all randomized patients, served as the supportive population for efficacy analysis. The per-protocol (PP) population included all randomized patients prior to experiencing a major protocol violation. The PK analysis set was a subset of the PP population and included patients having serial blood samples at scheduled times prior to and for 12 hours after the first administered dose of study drug. The safety population included all randomized patients who received at least 1 dose of study drug.

Demographic and baseline characteristics were summarized by treatment group with no inferential analyses performed. The primary analysis of the change from baseline in trough FEV₁ over the 12-week treatment period was performed in the FAS population using a mixed-model repeated measures (MMRM) analysis with effects due to baseline trough FEV₁, sex, age, visit, treatment, and visit-by-treatment interaction; this analysis did not include the open label comparator Fp DPI data. The primary comparison of Fp MDPI with placebo after 12 weeks of therapy was based on MMRM and supported by analysis of covariance model with effects due to baseline trough FEV₁, gender, age, and treatment with imputation of missing data based on the last on-therapy observation carried forward. Estimated treatment means and mean differences between each Fp MDPI dose and placebo at week 12 were provided with 95% confidence intervals (CIs) and corresponding *p* values. A comparison of each Fp MDPI dose or placebo MDPI with Fp DPI in the change from baseline in trough FEV₁ during and after the 12-week treatment period was also examined with MMRM and analysis of covariance.

Changes from baseline in weekly average of daily trough morning and evening PEF were analyzed in a similar manner as the primary endpoint, using MMRM. A marginal, or population-averaged, logistic model was used to analyze changes from baseline in the percentage of rescue-free 24-hour periods with covariates for sex, age, and treatment. Time to withdrawal due to meeting stopping criteria was compared between treatment groups using the log-rank test. Change from baseline in the ACT was evaluated over the 12-week treatment period without adjustment for multiplicity.

For PK analyses, pairwise comparisons of AUC_{0-t} and C_{max} between treatment groups were carried out using an analysis of variance model with a fixed factor for treatment. Comparisons were made among all Fp MDPI groups and between each Fp MDPI group and the Fp DPI group. The t_{max} and mean plasma concentration-vs-time profiles were summarized for each treatment group. All data were processed and summarized using SAS[®] software, version 9.2 (SAS Institute, Cary, NC).

Results

Patients

Of the 1903 patients screened for the study, 622 were randomized to treatment and received at least 1 dose of study drug from January 2012 to July 2013 (Figure 2). More patients in the placebo group (*n* = 41; 39%) withdrew early compared with the Fp MDPI dose groups (*n* = 12–24; 12%–23%) and the Fp DPI group (*n* = 20; 19%). Twenty patients in the placebo group met stopping criteria, compared with 4 to 9 patients treated with Fp MDPI (8, 7, 4, and 9 with Fp MDPI 12.5, 25, 50, and 100 µg, respectively) and 6 patients treated with Fp DPI. The probability of remaining in the study was substantially higher with all active treatments compared with placebo. Demographic and baseline characteristics of all randomized patients were comparable across treatment groups (Table 1).

Efficacy

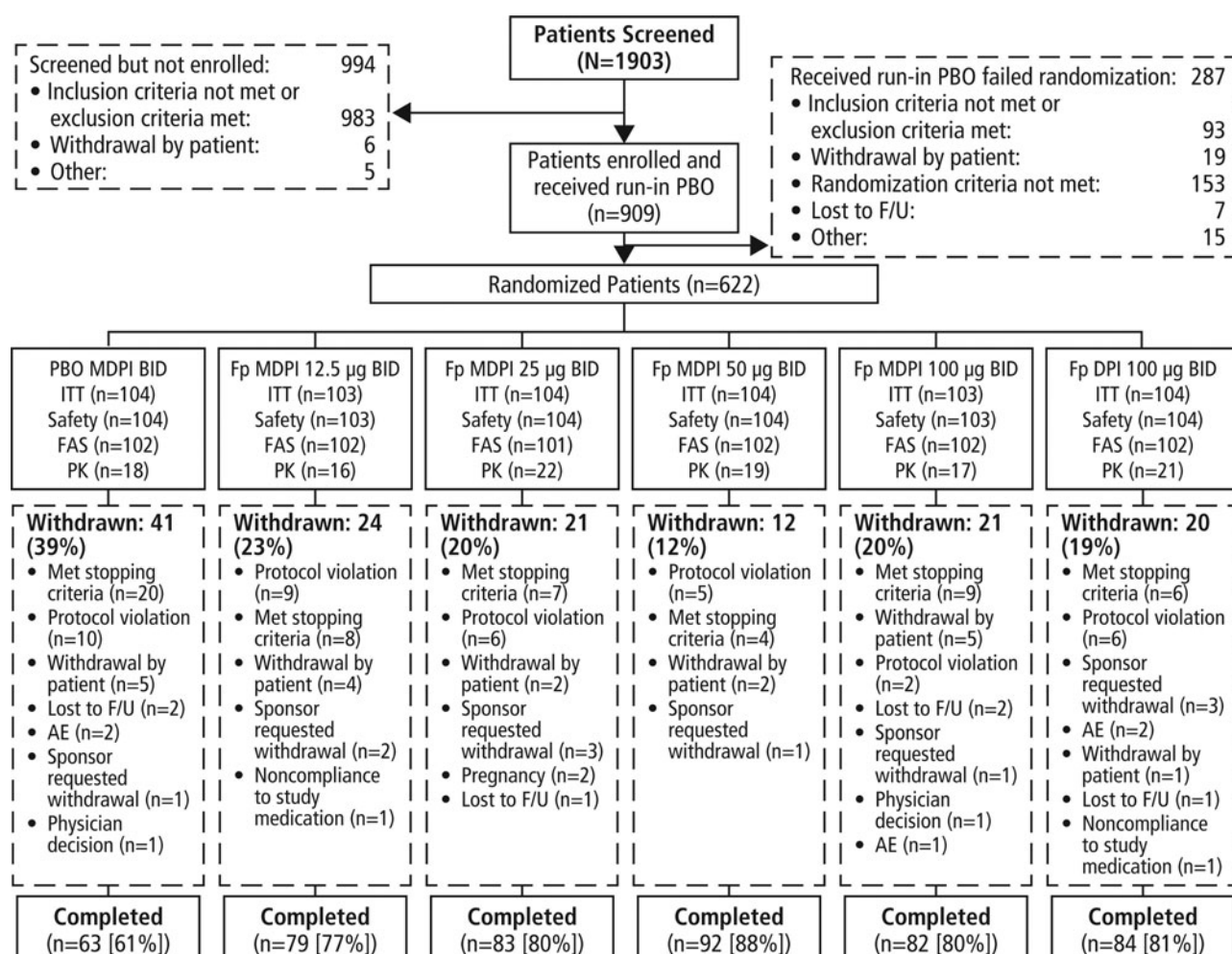
A total of 611 patients were included in the FAS. In all treatment groups, an increase in least squares (LS) mean FEV₁ from baseline was observed over the 12-week treatment period. Overall efficacy was demonstrated by the time-averaged dose response, which showed a significantly positive trend based on the linear in log-dose time-averaged trend test (*p* = 0.0001). The changes in FEV₁ were significantly greater (*p* < 0.01) in patients treated

Table 1. Patient demographics (all patients) and baseline characteristics (intent-to-treat population) by treatment group.

	Placebo MDPI BID (n = 104)	Fp MDPI BID				Fp DPI BID 100 µg (n = 104)	Total (N = 622)
		12.5 µg (n = 103)	25 µg (n = 104)	50 µg (n = 104)	100 µg (n = 103)		
Age, y							
Mean (SD)	40 (15)	41 (17)	42 (16)	39 (16)	37 (15)	40 (15)	40 (16)
Median (min, max)	38 (12, 77)	42 (12, 74)	45 (12, 78)	41 (12, 72)	35 (12, 73)	38 (12, 81)	40 (12, 81)
Sex, n (%)							
Female	55 (53)	57 (55)	63 (61)	60 (58)	60 (58)	63 (61)	358 (58)
Race, n (%)							
White	85 (82)	91 (88)	91 (88)	90 (87)	85 (83)	85 (82)	527 (85)
Black	17 (16)	10 (10)	11 (11)	12 (12)	14 (14)	17 (16)	81 (13)
Asian	0 (0)	1 (<1)	2 (2)	2 (2)	4 (4)	1 (<1)	10 (2)
Other ^a	2 (2)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)	4 (<1)
BMI, kg/m ²							
Mean (SD)	28 (7)	29 (7)	28 (6)	28 (7)	30 (8)	28 (7)	28 (7)
Predose FEV ₁ , L							
Mean (SD)	2.3 (0.62)	2.3 (0.69)	2.2 (0.59)	2.2 (0.63)	2.3 (0.66)	2.2 (0.66)	2.2 (0.64)
FEV ₁ reversibility (%)							
Mean (SD)	30.6 (17.84)	26.7 (12.01)	26.0 (11.86)	24.3 (10.63)	27.6 (12.92)	26.2 (12.50)	26.9 (13.25)

Note. BID, twice daily; BMI, body mass index; DPI, dry powder inhaler; FEV₁, forced expiratory volume in 1 second; Fp, fluticasone propionate; MDPI, multidose dry powder inhaler; SD, standard deviation.

^aIncludes American Indian, Alaskan Native, Portuguese, and Pacific Islander.

**Figure 2.** Patient disposition. AE, adverse event; BID, twice daily; DPI, dry powder inhaler; FAS, full analysis set; Fp, fluticasone propionate; F/U, follow-up; ITT, intent-to-treat; MDPI, multidose dry powder inhaler; PBO, placebo; PK, pharmacokinetics.

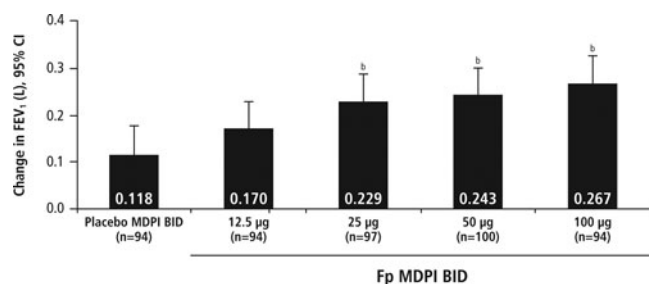


Figure 3. Least squares mean change in FEV₁ from baseline over 12 weeks (primary analysis using full analysis set [Fp DPI was excluded from the analysis as this was the primary analysis]; $n = 479$).^a BID, twice daily; CI, confidence interval; DPI, dry powder inhaler; FEV₁, forced expiratory volume in 1 second; Fp, fluticasone propionate; MDPI, multidose dry powder inhaler. Error bars represent 95% CI. ^a n denotes the number of patients who contributed at least once to the analysis. ^b $p < 0.01$ vs placebo MDPI.

with Fp MDPI 25, 50, and 100 µg (229–267 mL) compared with patients receiving placebo MDPI (118 mL) (Figure 3).

The difference in change from baseline FEV₁ was not significant for the lowest dose of Fp MDPI (12.5 µg twice daily) vs placebo ($p = 0.2227$). These results suggest a dose response for the Fp MDPI groups. The LS mean change in FEV₁ was increased in all treatment groups at all time points; this increase was substantial (appreciable) ($p \leq 0.0339$) compared with placebo in patients treated with Fp MDPI 50 and 100 µg at each time point from week 1 onwards, and in patients treated with Fp MDPI 25 µg at weeks 1, 4, and 12 ($p \leq 0.0286$) (Figure 4).

Patients treated with Fp DPI experienced a mean increase of 234 mL in FEV₁ from baseline over the 12-week study, which was substantially greater than placebo ($p < 0.01$; Figure 5). No substantial differences occurred

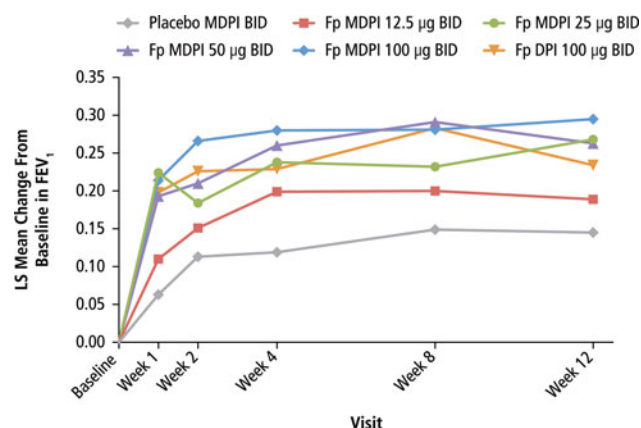


Figure 4. Least squares mean change in FEV₁ from baseline to weeks 1, 2, 4, 8, and 12 (full analysis set and Fp DPI 100 µg; $n = 611$). DPI, dry powder inhaler; FEV₁, forced expiratory volume in 1 second; Fp, fluticasone propionate; LS, least squares; MDPI, multidose dry powder inhaler.

between Fp DPI and any of the Fp MDPI dose groups. In addition, comparable efficacy was demonstrated by the 95% CIs for the 3 higher Fp MDPI dose groups (25, 50, and 100 µg), which were similar to those of the Fp DPI dose group for the increase in FEV₁ from baseline over the 12-week period (Figure 5).

Improvements in the weekly average of the daily trough morning and evening PEF over the 12-week treatment period were observed in all groups (Table 2). The increase in morning PEF was substantially greater than placebo (+9 L/min) for patients treated with Fp MDPI 12.5, 50, and 100 µg and Fp DPI (+31, 30, 28, and 27 L/min, respectively; all $p < 0.01$). The difference in evening PEF was substantially greater than placebo (+9 L/min) for patients treated with Fp MDPI 12.5 and 50 µg and Fp DPI (+28, 22, and 25 L/min, respectively; all $p < 0.05$). For both morning and evening PEF, there were no substantial differences between any of the Fp MDPI dose groups and the Fp DPI dose group.

For all treatment groups, mean ACT scores improved from baseline at all time points (weeks 4, 8, and 12), and the change in ACT from baseline over 12 weeks was substantially greater for all active treatment groups compared with the placebo group ($p < 0.02$ for all comparisons; Table 2). Among active treatment groups, the increase in ACT scores from baseline over the 12-week period was substantially greater following treatment with Fp DPI vs treatment with Fp MDPI at doses of 25 µg and 50 µg (both $p < 0.05$).

The percentage of rescue-free 24-hour periods increased in all treatment groups over the 12-week treatment period (Table 2). The increase was generally greater in the Fp MDPI groups (24%–34%) compared with the placebo group (21%), but a substantial increase was noted only for the 12.5-µg dose group ($p = 0.038$). Similar results were obtained for the percentage of symptom-free 24-hour periods (Table 2). In addition, the Fp MDPI groups were substantially more likely than the placebo group to remain in the study at week 12, with the times to withdrawal due to meeting stopping criteria for worsening asthma during this period being substantially prolonged in all Fp MDPI groups ($p < 0.01$). Withdrawal rates were similar among all Fp MDPI dose groups and Fp DPI.

Pharmacokinetics (PK subset population)

Pharmacokinetic parameters evaluated for 90 patients included in the PK analysis set (including 16–22 patients in each treatment group) are shown in Table 3. The t_{max} was similar across treatments, with a median ranging from 0.8 to 1.1 hours. Fluticasone propionate AUC_{0-t}

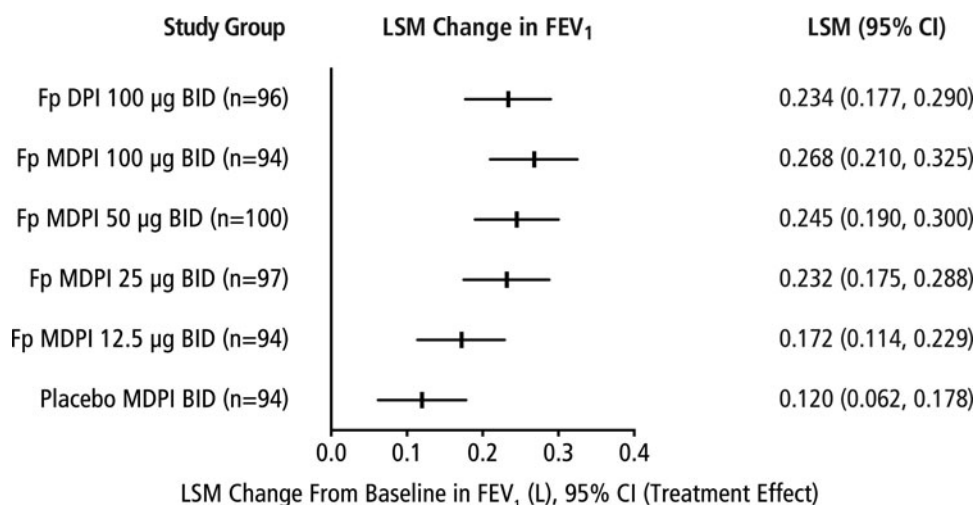


Figure 5. Mean change in FEV₁ from baseline over 12 weeks (MMRM analysis using full analysis set and Fp DPI 100 µg; $n = 575$).^a BID, twice daily; CI, confidence interval; DPI, dry powder inhaler; FEV₁, forced expiratory volume in 1 second; Fp, fluticasone propionate; LSM, least squares mean; MDPI, multidose dry powder inhaler; MMRM, mixed-model repeated measures. ^a n denotes the number of patients who contributed at least once to the analysis.

and C_{max} increased approximately proportionally with increasing doses of Fp. Systemic exposure from Fp DPI 100 µg was higher than that from Fp MDPI 25 and 50 µg but lower than that from Fp MDPI 100 µg.

Safety

The overall incidence of AEs was similar across all 6 treatment groups during the active treatment period. The most commonly occurring AEs included nasopharyngitis, upper respiratory tract infection, and headache, and are summarized in Table 4. Adverse events of particular interest for inhaled corticosteroids occurred infrequently

in ≤ 3 patients (generally $<1\%$) in any treatment group (Table 4).

There were no deaths during the study. Five patients discontinued the study due to AEs, including 1 patient in the Fp MDPI 100 µg group and 2 patients each in the placebo and Fp DPI groups. There were 8 serious AEs in 7 patients: migraine ($n = 1$) in the Fp MDPI 50 µg group, hypertension ($n = 1$) and uterine hemorrhage and anemia ($n = 1$) in the Fp MDPI 100 µg group, anaphylactic shock ($n = 1$) and groin abscess ($n = 1$) in the Fp DPI group, and hypovolemia ($n = 1$) and exacerbation of asthma ($n = 1$) in the placebo group. None of the serious AEs was considered to be related to Fp MDPI. No clinically meaningful

Table 2. Additional efficacy outcomes by treatment group.

Change from baseline over 12-week treatment period	Fp MDPI BID					
	Placebo MDPI BID ($n = 102$)	12.5 µg ($n = 102$)	25 µg ($n = 101$)	50 µg ($n = 102$)	100 µg ($n = 102$)	Fp DPI BID 100 µg ($n = 102$)
Morning PEF, L/min						
LS mean (SE) ^a	9.26 (4.76)	30.99 (4.60) ^b	21.01 (4.52)	29.58 (4.40) ^b	27.55 (4.61) ^b	26.96 (4.50) ^b
Evening PEF, L/min						
LS mean (SE) ^a	9.42 (4.59)	27.65 (4.47) ^b	18.69 (4.35)	22.20 (4.24) ^c	20.48 (4.49)	24.95 (4.36) ^c
ACT ^a						
LS mean (SE)	2.39 (0.38)	4.36 (0.35) ^d	3.76 (0.34) ^b	3.65 (0.33) ^c	3.98 (0.34) ^b	4.78 (0.35) ^d
Probability of study retention at week 12 (95% CI)	0.5655 (0.4528, 0.6636)	0.8041 (0.7067, 0.8720) ^d	0.7895 (0.6927, 0.8589) ^d	0.9077 (0.8300, 0.9509) ^d	0.7657 (0.6660, 0.8392) ^b	0.8272 (0.7332, 0.8905) ^d
Percentage of rescue-free 24-hour periods ^a						
Mean (SE)	21.30 (4.67)	34.08 (3.91) ^c	31.76 (4.23)	28.06 (3.80)	24.07 (4.28)	29.82 (4.19)
Percentage of symptom-free 24-hour periods ^a						
Mean (SE)	21.15 (4.59)	35.50 (4.01) ^c	28.42 (4.06)	26.91 (3.85)	29.39 (4.23)	35.22 (4.25)

Note. ACT, Asthma Control Test; BID, twice daily; DPI, dry powder inhaler; Fp, fluticasone propionate; LS, least squares; MDPI, multidose dry powder inhaler; PEF, peak expiratory flow; SE, standard error.

^aFp DPI is based on the full model including all data; placebo and Fp MDPI are based on the model excluding Fp DPI.

^b $p < 0.01$ vs placebo.

^c $p < 0.05$ vs placebo.

^d $p \leq 0.001$ vs placebo.

Table 3. Pharmacokinetic parameters among pharmacokinetic analysis set ($n = 90$).

	Fp MDPI BID				Fp DPI BID
	12.5 µg ($n = 14$)	25 µg ($n = 22$)	50 µg ($n = 19$)	100 µg ($n = 16$)	100 µg ($n = 19$)
t_{max} , hr					
Median	1.1	1.0	1.0	0.8	1.0
Min, max	(0.2, 4.0)	(0.1, 12.0)	(0.3, 12.0)	(0.2, 4.0)	(0.3, 12.0)
AUC_{0-t} , pg·hr/mL					
Mean (SD)	21.6 (27.1)	42.0 (23.2)	63.2 (22.6)	153.8 (91.4)	103.4 (45.7)
Geometric mean ratio ^a	0.133	0.364	0.620	1.394	
95% CI	0.081, 0.217	0.235, 0.564	0.394, 0.975	0.868, 2.238	
C_{max} , pg/mL					
Mean (SD)	5.4 (4.2)	10.0 (5.4)	12.9 (5.1)	33.6 (15.5)	23.4 (10.7)
Geometric mean ratio ^a	0.213	0.422	0.561	1.429	
95% CI	0.152, 0.297	0.313, 0.567	0.413, 0.763	1.036, 1.971	

Note. AUC_{0-t} , area under the plasma concentration-vs-time curve from time zero to the time of the last quantifiable concentration; BID, twice daily; CI, confidence interval; C_{max} , maximum observed plasma concentration; DPI, dry powder inhaler; Fp, fluticasone propionate; MDPI, multidose dry powder inhaler; SD, standard deviation; t_{max} , time of maximum observed plasma concentration.

^aFp MDPI vs Fp DPI.

trends in mean changes from baseline for any clinical laboratory variable were observed, and no safety signals were associated with vital signs or electrocardiogram findings.

Discussion

Fluticasone propionate MDPI was evaluated at 4 dosage strengths in this dose-ranging, active- and placebo-controlled study. Overall efficacy was demonstrated by the time-averaged dose-response, which showed a significantly positive trend based on the linear in log-dose time-averaged trend test ($p = 0.0001$). The primary efficacy variable of change from baseline in trough FEV₁ over the 12-week treatment period was significantly ($p < 0.01$) greater in patients treated with Fp MDPI 25, 50, and 100 µg compared with patients receiving placebo.

The effect of Fp MDPI on FEV₁ was observed within the first week and generally increased at all time points through week 12. The mean increase in FEV₁ observed from baseline over the 12-week treatment period with active comparator Fp DPI 100 µg was intermediate between those for the Fp MDPI 25 and 50 µg doses. In a study conducted by Wasserman et al, patients with mild-to-moderate asthma treated with Fp Diskhaler (50, 100, or 250 µg twice daily) experienced significantly ($p < 0.001$) improved morning pre-dose FEV₁ compared with patients receiving placebo over the 12-week study, with no significant difference between treatment groups, supporting the efficacy results of the present study across the doses evaluated [10].

Secondary efficacy outcomes also support comparable efficacy of Fp MDPI and Fp DPI on asthma symptoms,

Table 4. Incidence of adverse events occurring in any treatment group; safety population.

MedDRA preferred term, n (%)	Placebo MDPI BID ($n = 104$)	Fp MDPI BID				Fp DPI BID 100 µg ($n = 104$)
		12.5 µg ($n = 103$)	25 µg ($n = 104$)	50 µg ($n = 104$)	100 µg ($n = 103$)	
All adverse events occurring in ≥ 3 patients	31 (30)	31 (30)	32 (31)	36 (35)	37 (36)	32 (31)
Nasopharyngitis	5 (5)	4 (4)	5 (5)	7 (7)	3 (3)	1 (<1)
Upper respiratory tract infection	3 (3)	7 (7)	2 (2)	3 (3)	5 (5)	4 (4)
Headache	3 (3)	5 (5)	5 (5)	3 (3)	4 (4)	5 (5)
Hypertension	1 (<1)	1 (<1)	1 (<1)	1 (<1)	3 (3)	3 (3)
Toothache	1 (<1)	0	0	0	2 (2)	4 (4)
Sinusitis	1 (<1)	0	3 (3)	1 (<1)	2 (2)	0
Bronchitis	0	1 (<1)	0	3 (3)	0	1 (<1)
Otitis media	0	3 (3)	0	0	2 (2)	0
Viral upper respiratory tract infection	0	0	1 (<1)	1 (<1)	3 (3)	1 (<1)
Back pain	0	0	1 (<1)	3 (3)	3 (3)	0
Adverse events of interest for inhaled corticosteroids						
Pneumonia ^a	0	0	1 (<1)	0	1 (<1)	0
Oral candidiasis	0	0	1 (<1)	0	0	1 (<1)
Pharyngitis	0	1 (<1)	2 (2)	1 (<1)	0	0
Oropharyngeal pain	1 (<1)	3 (3)	0	1 (<1)	1 (<1)	2 (2)
Throat irritation	0	0	0	0	0	1 (<1)

Note. BID, twice daily; DPI, dry powder inhaler; Fp, fluticasone propionate; MDPI, multidose dry powder inhaler; MedDRA, Medical Dictionary for Regulatory Activities.

^aPneumonia and lobar pneumonia combined.

demonstrated by improvements in morning and evening PEF and the probability of staying in the study with active treatment. This difference in treatment retention between the active treatment and placebo groups emphasizes the importance of treatment efficacy in patient adherence to asthma treatment regimens.

The improvements in pulmonary function, asthma control, ACT score, and asthma symptoms were also, in most cases, accompanied by substantial improvements from baseline in rescue-medication use and symptom-free time compared with placebo.

The rates of AEs were similar across treatment groups, without any evidence of a dose relationship. The discontinuation rate due to AEs was low and distributed across the Fp MDPI 100 µg, Fp DPI 100 µg, and placebo groups. Serious AEs occurred in approximately 1% of patients, with similar frequency across the placebo and active treatment groups. The safety profile of Fp MDPI at dosages of 12.5, 25, 50, and 100 µg was similar to the established profile of Fp DPI, and no new safety signals were observed.

The pharmacokinetic parameters AUC_{0-t} and C_{max} of Fp also increased with increasing doses of Fp MDPI in an approximately dose-proportional manner. When normalized by dose, the systemic exposure of Fp from the MDPI was consistently higher than that of Fp delivered by DPI, suggesting that the administration of the drug via an MDPI is more effective compared with a DPI. Although the systemic exposure of Fp from Fp MDPI 25 and 50 µg was consistently lower than that from Fp DPI 100 µg, the clinical efficacy, as shown by improvements in FEV₁ with Fp MDPI 25 and 50 µg, was comparable to Fp DPI 100 µg. In a similar study conducted in healthy adults, the systemic exposure (i.e., C_{max} and AUC_{0-t}) following single inhaled doses of Fp was approximately 2-fold higher for patients treated with Fp MDPI 400 µg total dose compared with Fp Diskus 400 µg total dose [7]. In a study conducted by Gillespie et al, the systemic exposure to Fp in healthy adults treated with single doses of Fp MDPI 800 µg was comparable to exposure with Fp Diskus 1000 µg [8]. The more efficient drug delivery with the MDPI allows for the use of a lower dose of Fp with comparable efficacy, as shown in the present study. Lower doses of Fp reduce the risk of AEs and adhere to guidelines recommending the minimum medication necessary to maintain control.

The 12-week dose-ranging design of this study allowed observation of benefits and risks across varied steady-state and maintenance doses of Fp MDPI and compared these outcomes with those of placebo and Fp DPI. The PK parameters evaluated as part of this study provided additional useful information on systemic exposure following administration of Fp via the novel MDPI or traditional DPI. However, administration of Fp DPI was not

blinded. The study population was limited to patients with uncontrolled persistent asthma not previously treated with inhaled corticosteroid medications. A recent study assessed the benefits of Fp MDPI in patients receiving prior ICS over a broader range of asthma severity (ClinicalTrials.gov identifier: NCT01576718).

Conclusions

The results of this dose-ranging study support Fp MDPI 25 and 50 µg, administered twice daily, as safe and efficacious doses for further evaluation in clinical assessments as part of the Fp MDPI development program.

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Declaration of interest

Dr. Kerwin has served on advisory boards and speaker panels for and has received travel reimbursement from Amphastar, AstraZeneca (Pearl), Forest, Ironwood, Merck, Mylan, Novartis, Pfizer, Sanofi-Aventis, Sunovion, Targacept, Teva, and Theravance. He has conducted multicenter clinical research trials for approximately 40 pharmaceutical companies. Dr. Song and Mr. Gillespie are employees of Teva Pharmaceuticals. Dr. Steinfeld was a full-time employee of Teva Pharmaceuticals during study conduct and analysis.

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