



Once-daily fluticasone furoate is efficacious in patients with symptomatic asthma on low-dose inhaled corticosteroids

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ABSTRACT

Background: Fluticasone furoate (FF) is an inhaled corticosteroid (ICS) with 24-hour activity in development as a once-daily treatment for the long-term management of asthma.

Objective: To assess the efficacy and safety of 4 doses of once-daily FF administered using a dry powder inhaler in patients (≥ 12 years) with moderate asthma, uncontrolled on low-dose ICS (fluticasone propionate [FP] 200 $\mu\text{g}/\text{day}$ or equivalent).

Methods: This double-blind, placebo-controlled, dose-ranging study randomized 622 patients to 1 of 6 treatments: FF (100, 200, 300, or 400 μg) once daily in the evening, FP 250 μg twice daily (active control), or placebo for 8 weeks. The primary endpoint was the change from baseline in predose evening forced expiratory volume in 1 second (FEV_1) at week 8.

Results: At week 8, relative to placebo, all doses of FF once daily and FP twice daily demonstrated significantly ($P < .001$) greater increases from baseline and greater than 200-mL increases in predose FEV_1 . There was no evidence of a dose-response relationship between FF doses. Improvement with once-daily FF was similar to or greater than that for twice-daily FP. Secondary efficacy endpoint findings generally supported the efficacy of FF 100 to 400 μg once daily, although statistically significant improvements versus placebo in symptom-free 24-hour periods were only reported for FF 400 μg . There were few withdrawals due to lack of efficacy. Oral candidiasis was reported in 0 to 4% of patients; 24-hour urinary cortisol excretion ratios were similar across active treatment groups and not significantly different from placebo.

Conclusion: FF 100 to 400 μg once daily in the evening is effective and well tolerated in patients with asthma uncontrolled on low-dose ICS, with 100 μg and 200 μg , considered the most applicable doses in this asthma population.

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Introduction

Inhaled corticosteroids (ICSs) are considered to be the most effective therapy for long-term control of mild persistent asthma^{1–3} as monotherapy or in combination with a long-acting beta₂ agonist (LABA) for more severe disease. ICSs reduce symptoms, improve lung function, decrease bronchial hyperresponsiveness, may prevent airway remodeling, and are associated with prevention of asthma exacerbations and reduced asthma mortality.^{4–8} Despite this, asthma control remains suboptimal in a significant proportion of patients.⁹

Poor adherence is a frequent cause of inadequate asthma control,^{2,10,11} and it is known that adherence increases with less frequent dosing¹² such that once-daily dosing is associated with higher adherence than twice-daily dosing.^{13,14} Indications for once-daily ICS dosing in asthma are limited; therefore, there is a need for once-daily ICSs for all levels of asthma severity, which also offer potential combination with an LABA in a fixed-dose once-daily combination. Asthma symptoms can be worse at night, and this, in addition to circadian fluctuations in cortisol levels, appears to favor evening dosing.^{15–17} Indeed, clinical studies have shown that once-daily dosing of ICSs in the evening is at least as¹⁸ if not more^{19,20} effective (in terms of improvements in lung function outputs) as once-daily dosing in the morning. Fluticasone furoate (FF) is a novel ICS with activity maintained for 24 hours post inhalation.²¹ It is under development for asthma as a monotherapy and as combination therapy with vilanterol for once-daily ICS/LABA therapy in asthma and chronic obstructive pulmonary disease (COPD). FF is distinct from fluticasone propionate (FP), with a 2-furoic acid ester replacing the simpler propionate ester at the 17 α pocket.²² This results in greater occupancy and affinity for the glucocorticoid receptor and longer retention in respiratory tissues than FP.^{22,23}

The aim of this study was to assess the efficacy, safety, and tolerability of 4 doses of FF administered once daily in the evening in patients with moderate asthma uncontrolled on low-dose ICSs. Twice-daily FP (250 μ g) was used as an appropriate active control. Some of the results of this study have been presented in abstract form.²⁴

Methods

Design

An 8-week, phase IIb, multicenter, international, randomized, double-blind, double-dummy, parallel-group, placebo-controlled study (GlaxoSmithKline study number: FFA109685; clinicaltrials.gov: NCT00603278) conducted at 144 centers. This study was part of a large phase II program to help identify suitable doses of FF across a range of asthma severities for development as a monotherapy and as part of a fixed-dose ICS/LABA combination.

Patients

Patients were 12 years of age or older with moderate persistent symptomatic asthma² while receiving low-dose ICS therapy. Inclusion criteria included reversibility to albuterol (increase in baseline forced expiratory volume in 1 second [FEV₁] of 12% or greater and 200 mL or greater), pre-bronchodilator FEV₁ of 40 to 90% predicted (for evening clinic visits) or 40 to 85% predicted (for morning visits), and maintenance ICS therapy for 8 weeks or longer (stable dose $\geq$ 4 weeks) before screening. National Health and Nutrition Examination Survey III predicted FEV₁ values were used, with adjustments made for African American patients.²⁵ Key exclusion criteria and nonpermitted medications are presented in eSupplements 1 and 2.

The study was approved by local ethics review committees and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all patients.

Treatments

Patients were randomized (1:1:1:1:1) to receive 8 weeks' therapy with FF 100, 200, 300, or 400 μ g administered once daily in the evening using a dry powder inhaler (DPI) plus placebo administered twice daily via Diskus/Accuhaler; FP 250 μ g twice daily via Diskus/Accuhaler plus placebo once daily (evening) via DPI; or placebo once daily (evening) via DPI, plus placebo twice daily via Diskus/Accuhaler (eFig 1). The central randomization schedule was generated by the sponsor using a validated computerized system (RandAll; GlaxoSmithKline, London, United Kingdom). Patients were randomized using Registration and Medication Ordering System (RAMOS; GlaxoSmithKline), an automated, interactive telephone-based system, used by the investigator or designee to register and randomize the patient and receive medication assignment information. Spirometry was performed at screening, on day 1 (randomization) and at each clinic visit during the treatment period (days 7–56).

Study medications were blinded to both investigators and study patients and were identical in appearance for all treatment groups.

Efficacy

The primary efficacy endpoint was mean change from baseline in evening predose, prebronchodilator (trough) FEV₁ (hereafter referred to as predose FEV₁) after 8 weeks' treatment. Secondary endpoints included mean change from baseline in daily morning and evening predose, prebronchodilator peak expiratory flow (PEF) averaged over 8 weeks, percentage of symptom-free and rescue-free 24-hour periods, and withdrawals attributable to lack of efficacy.

Safety

Safety and tolerability assessments included incidence of adverse events (AEs), oropharyngeal examination, laboratory tests, 24-hour urinary cortisol excretion, and vital signs. Blood and urine samples were analyzed at a central laboratory. Patients who had asthma exacerbations (defined as any worsening of asthma that required any treatment other than study medication or rescue albuterol) were withdrawn from the study.

Statistics

The primary treatment comparison was a test for a linear dose-response in evening predose FEV₁ at week 8 across the doses of FF and placebo. If statistically significant, each FF dose was compared with placebo. Comparisons were made on the intent-to-treat (ITT) population (all randomized patients who received at least one dose of study medication) using analysis of covariance (adjusted for baseline, age, sex, country, and treatment group) and the last observation carried forward method to impute missing data. For secondary endpoints, an analysis of covariance model (adjusted for baseline, age, sex, country, and treatment group) was used to analyze change from baseline values.

The goal was to have 99 evaluable patients in each arm to provide approximately 96% power to detect a slope of 0.5 mL/ μ g in the change from baseline in predose FEV₁ (an effect of 200 mL improvement per 400 μ g FF) assuming a standard deviation of 430 mL and a 5% significance level (2-sided). The study had 90% power to detect a 200-mL difference in pairwise comparisons of change from baseline in predose FEV₁ between any active dose and placebo.

Results

Patient characteristics

Of 1,406 screened patients, 622 patients were randomized to study treatment, and 615 received at least 1 dose of study medication (ITT population; Fig 1). Demographic characteristics were similar across study groups (Table 1).

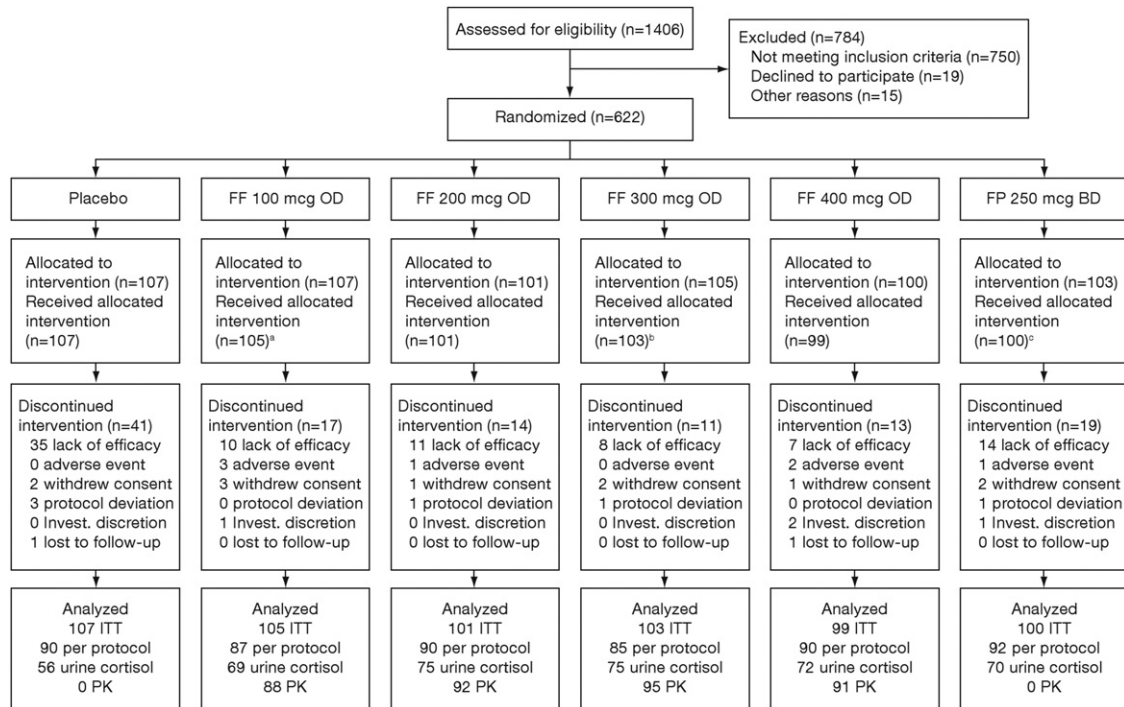


Fig. 1. Patient disposition. ^a*n* = 2, ^b*n* = 2, ^c*n* = 3 patients who failed screening but were still randomized. BD, twice daily; FF, fluticasone furoate; FP, fluticasone propionate; ITT, intent-to-treat; OD, once daily; PK, pharmacokinetic.

Efficacy

A statistically significant ($P < .001$) linear trend test indicated the dose–response relationship slope across all once-daily FF treatment groups and placebo was not zero (Table 2). Two-sided tests of each dose versus placebo demonstrated superiority of all active

treatments relative to placebo. The test for linear trend excluding placebo was not significant ($P = .107$, estimate of slope 0.278 mL/μg), indicating no dose–response between the FF doses tested.

At week 8, all active treatment groups demonstrated significant placebo-adjusted improvements from baseline in predose FEV₁

Table 1
Demographics and baseline characteristics (ITT population)

	Placebo (N = 107)	FF 100 μg OD (N = 105)	FF 200 μg OD (N = 101)	FF 300 μg OD (N = 103)	FF 400 μg OD (N = 99)	FP 250 μg BD (N = 100)
Age (years)						
Mean (range)	39.1 (12–75)	38.3 (12–77)	38.8 (12–72)	39.9 (12–80)	40.7 (12–78)	39.8 (12–79)
Sex, n (%)						
Female	74 (69)	72 (69)	63 (62)	67 (65)	64 (65)	62 (62)
Race, n (%)						
White	62 (58)	64 (61)	65 (64)	63 (62)	56 (57)	61 (61)
African American/African	5 (5)	2 (2)	0	2 (2)	4 (4)	3 (3)
Asian	26 (24)	25 (24)	23 (23)	23 (23)	25 (25)	23 (23)
Other/mixed race	14 (13)	14 (13)	13 (13)	14 (14)	14 (14)	13 (13)
Screening lung function, mean (SD)						
Pre-bronchodilator FEV ₁ (L)	2.083 (0.6441)	2.130 (0.7054)	2.145 (0.6335)	2.136 (0.5794)	2.120 (0.5992)	2.199 (0.5948)
Pre-bronchodilator FEV ₁ (% predicted)	66.59 (12.571)	66.68 (11.744)	66.38 (12.581)	66.74 (11.251)	66.92 (10.733)	69.26 (10.793)
Reversibility in FEV ₁ (%)	29.15 (19.972)	26.42 (12.689)	29.25 (16.631)	26.10 (13.623)	28.94 (17.146)	25.70 (14.310)
FEV ₁ at baseline (L), mean	2.228	2.284	2.296	2.251	2.315	2.300
DRC data at baseline, mean						
PM PEF (L)	337.0	330.9	336.6	347.5	363.5	358.3
AM PEF (L)	327.9	319.1	330.1	331.1	351.1	347.8
Rescue-free 24-hour periods (%)	14.0	13.8	17.3	12.2	12.9	15.1
Symptom-free 24-hour periods (%)	7.4	13.1	9.4	11.5	7.7	8.8
Baseline ICS and maximum allowable dose [μg], mean (range)						
FP [250], N = 227	199 (88–250)	214 (88–440)	225 (125–250)	220 (100–500)	220 (125–250)	215 (100–250)
Budesonide [400], N = 193	366 (180–400)	336 (180–400)	372 (200–400)	374 (200–400)	365 (180–400)	357 (180–400)
Beclomethasone dipropionate [500 DPI; 200 HFA], N = 150	198 (80–500)	201 (80–500)	193 (100–500)	205 (80–500)	186 (80–400)	238 (80–500)
Mometasone [220], N = 25	214 (200–220)	220 (220–220)	220 (220–220)	213 (200–220)	216 (200–220)	210 (200–220)
Ciclesonide [200], N = 13	160 (160–160)	160 (160–160)	160 (160–160)	170 (160–200)	160 (160–160)	160 (160–160)
Triamcinolone [1,000], N = 4	–	400 (400–400)	400 (400–400)	–	–	138 (75–200)
Flunisolide [1,000], N = 1	–	500 (500–500)	–	–	–	–

Abbreviations: BD, twice daily; DRC, daily record card; DPI, dry powder inhaler; FF, fluticasone furoate; FEV₁, forced expiratory volume in 1 second; FP, fluticasone propionate; HFA, hydrofluoroalkane inhaler; ICS, inhaled corticosteroid; ITT, intent-to-treat; OD, once daily; PEF, peak expiratory flow.

Table 2
Linear trend test and statistical analysis of change from baseline in predose FEV₁ at week 8 (last observation carried forward) (ITT population)

		Placebo (N = 107)		FF				FP
				100 µg OD (N = 105)	200 µg OD (N = 101)	300 µg OD (N = 103)	400 µg OD (N = 99)	250 µg BD (N = 100)
Linear trend (including placebo)								
P value		<.001						
Estimate of slope		0.646 mL/µg						
95% CI		0.391, 0.900						
LS mean (L)		2.215	2.422	2.453	2.508	2.494	2.440	
LS mean change (mL)		−65	142	173	228	215	160	
Difference vs. placebo								
LS mean difference (mL)			207	238	293	279	225	
95% CI			96, 318	127, 349	182, 404	167, 392	114, 337	
P value			<.001	<.001	<.001	<.001	<.001	

Abbreviations: BD, twice daily; CI, confidence interval; FF, fluticasone furoate; FP, fluticasone propionate; ITT, intent-to-treat; LS, least squares; OD, once daily.

($P < .001$; Fig. 2) and achieved the predefined 200 mL difference from placebo. Improvements with FF were similar to or greater than those reported for twice-daily FP (Table 2). The treatment interaction with each of the covariates modeled was not statistically significant. Similar results were obtained for the per-protocol population (data not shown).

Morning and evening predose PEF values over weeks 1 through 8 were also significantly different from placebo, indicating greater improvement with therapy (eFig 2 and eTable 1); separation between active treatment and placebo was evident from days 1 and 2. Mean symptom- and rescue-free 24-hour periods increased over 8 weeks in all groups. Significant improvements in symptoms were observed with FF 400 µg once daily and FP 250 µg twice daily, and for rescue use with all treatments except FF 200 µg once daily (eTable 2). Withdrawals attributable to lack of efficacy were significantly ($P < 0.001$) greater with placebo (33%) compared with all FF treatment groups (10%, 11%, 8%, and 7% for 100, 200, 300, and 400 µg, respectively) and twice-daily FP 250 µg (14%; $P = .002$) (Fig 3).

Safety

On-treatment AEs were reported in 33 to 41% of patients across the FF groups, 42% with FP and 30% with placebo (eTable 3). The most commonly reported on-treatment AEs were headache (6–9% across treatment groups) and nasopharyngitis (4–9%). No dose-related increases in the frequency of the most common AEs were observed.

No deaths were reported. Four serious AEs were reported, 2 during the pretreatment period (infective colitis [subsequently randomized to placebo group]; knee injury [subsequently randomized to FF 400 µg group]) and 2 on treatment (suspected myocardial infarction [FF 300 µg group]; asthma exacerbation [FF 400 µg group]). All were considered unrelated to study medication. Treatment-related AEs were reported in 6 to 11% of patients across the

active treatment groups (highest with FF 300 µg and FP, both 11%), versus less than 1% with placebo. Seven patients experienced AEs leading to withdrawal, 3 of these (pharyngitis and throat irritation [both FF 100 µg group]; bilateral thigh pain [FF 400 µg group]) were considered possibly related to study treatment.

The incidence of oral/oropharyngeal candidiasis across the FF groups was less than 1 to 4%, 4% with FP 250 µg, and 0% with placebo. There were no significant differences in 24-hour urinary cortisol excretion ratios between the FF, FP, and placebo groups (eFigs 3 and 4). Shifts from the normal range at baseline to below the lower limit of normal for 24-hour urinary cortisol excretion at week 8 was 3% for placebo, 0%, 4%, 7%, and 1%, respectively, for once-daily FF 100, 200, 300, and 400 µg, and 1% for twice-daily FP 250 µg. Asthma exacerbations were experienced by 6 patients receiving placebo, 4 receiving FF 100 µg, 3 receiving FF 200 µg, 2 receiving FF 400 µg, and 5 receiving FP 250 µg. No safety concerns were raised by the results of vital sign monitoring or laboratory testing, and no treatment-related changes were seen.

Discussion

The results from this study support the 24-hour duration of effect of a single daily dose of FF compared with twice-daily dosing of FP. All doses of once-daily FF significantly improved the predose evening FEV₁ from baseline relative to placebo at week 8. The difference from placebo in predose FEV₁ ranged from 207 mL (FF 100 µg) to 293 mL (FF 300 µg), with no evidence of a dose response. Efficacy was generally similar to twice-daily FP, but numerically better for all FF doses greater than 100 µg.

As a clinical measure, FEV₁ in adults reflects asthma severity and correlates with symptoms and healthcare utilization.^{26,27} It is well validated, reproducible,^{26,28,29} and is an important element in defining asthma control.^{1,12,30} It is regarded as superior to PEF as an index of improvement in airway caliber.³¹ The lack of a dose–

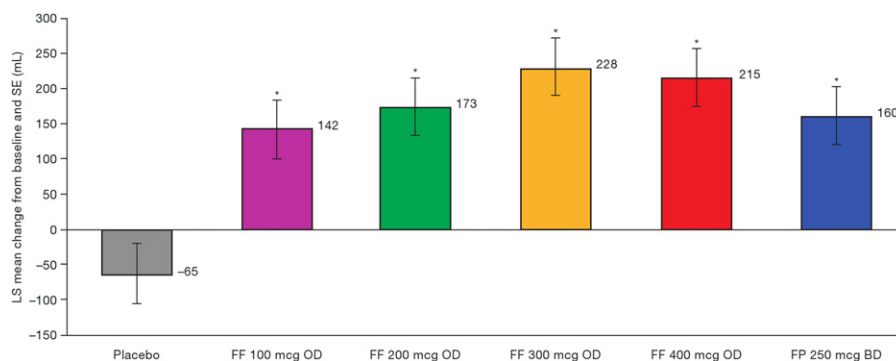


Fig. 2. Least squares (LS) mean change from baseline in pre dose FEV₁ (last observation carried forward) at week 8 (ITT population). * $P < .001$ relative to placebo. BD, twice daily; FF, fluticasone furoate; FP, fluticasone propionate; ITT, intent-to-treat; OD, once daily; SE, standard error.

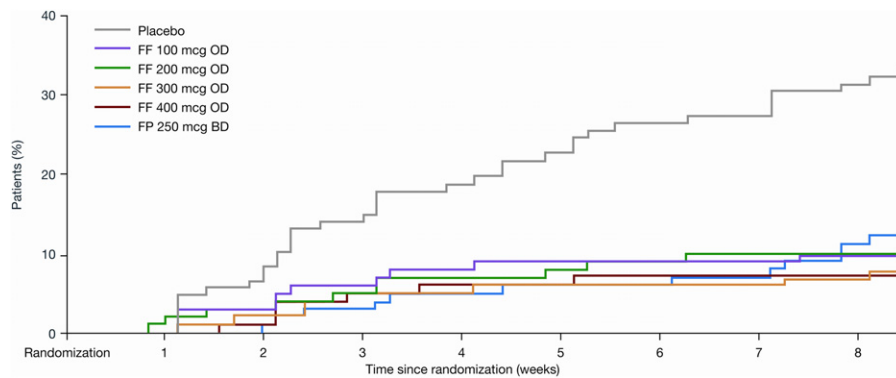


Fig. 3. Withdrawals due to lack of efficacy (cumulative incidence) (ITT population). BD, twice daily; FF, fluticasone furoate; FP, fluticasone propionate; ITT, intent-to-treat; OD, once daily.

response relationship (but significant efficacy vs placebo) for FF on predose FEV₁ in this study is consistent with results of early studies conducted with twice-daily FP.^{32,33} The FEV₁ dose–response curve of any ICS in mild-to-moderate asthma is shallow,³⁴ and most effect on FEV₁ and other endpoints is observed with doses of FP less than 200 μ g/day.³⁵ The FF doses investigated here may be near the top of the dose–response curve for the FEV₁ endpoint. In dose-ranging studies similar in design to this one, FF demonstrated dose-related efficacy across lower doses (25–200 μ g) in steroid-free mild/moderate asthma³⁶ and efficacy, but no dose–response relationship for higher doses (200–800 μ g) in more severe asthma.³⁷ It may be possible to differentiate the effects of higher ICS doses with other endpoints such as exacerbation frequency, provocation, or biomarker analysis (e.g. adenosine monophosphate challenge or fraction of exhaled nitric oxide); therefore, other efficacy endpoints need to be assessed to more fully characterize the effects of FF treatment.

The relatively flat dose–response for ICS found in this and other studies has important implications for asthma management.^{34,35} In stable persistent asthma, there may be a low corticosteroid threshold above which ICS doses produce relatively small therapeutic benefits.³⁸ From these data the threshold FF dose appears to be less than 100 μ g; however, at a much higher corticosteroid doses than this, there is no evidence of adrenal suppression, suggesting an excellent therapeutic index. Some patients appear to be more corticosteroid responsive, and symptoms and airway inflammation (eosinophils) may be reduced by ICS doses below and up to this “threshold.” These asthma patients correspond to the mild to moderate asthma clusters (I and II) recently described by the National Heart, Lung and Blood Institute Severe Asthma Research Program.²⁸ Patients with moderate persistent asthma who are not controlled at this threshold dose may be more responsive to the introduction of an additional controller therapy such as a LABA, than to increasing the dose of ICS.^{39–43}

Improvements in evening and morning predose PEF and rescue-free/symptom-free 24-hour periods supported those observed with FEV₁. The finding that only the 400 μ g dose of FF and FP 250 μ g significantly improved symptom-free 24-hour periods relative to placebo is interesting and may relate to the higher than expected placebo response observed. Potentially, the high number of withdrawals from the placebo group because of a lack of efficacy resulted in a largely “asymptomatic” placebo population at this analysis endpoint. Additionally, although improvement was only observed at the highest FF dose used (400 μ g), results from a separate study in patients symptomatic on nonsteroid asthma therapy showed significant improvements in both rescue-free and symptom-free 24-hour periods at FF doses of 50 to 200 μ g.³⁶

FF was well tolerated, with an AE incidence similar across active treatment groups and no evidence of relation to dose. Serious AEs

were uncommon and considered unrelated to treatment, and ICS-associated AEs, including oral candidiasis and dysphonia, were low. FF had little effect on urinary cortisol, with no significant differences in cortisol excretion ratios between any FF dose and placebo. Data from studies of longer duration are required to properly assess any potential effect in patients treated with FF.

This study had a number of important strengths, including the placebo-controlled parallel-group design, large number of patients, and variety of efficacy endpoints. Use of twice-daily FP 250 μ g was an active control appropriate for this population. Although not powered to directly compare FP with FF, there were similarities in the therapeutic responses between these 2 treatments, supporting efficacy of once-daily dosing with FF. Limitations of the study included the high withdrawal rate with placebo and 8-week duration of treatment. However, although results from an 8-week study cannot be used to make generalizations regarding long-term treatment effects (and this was not the intention of the study), this duration was considered sufficiently long to demonstrate the efficacy and safety of FF and to identify the dose(s) of FF suitable for evaluation in phase III trials. Furthermore, the treatment effects reported during weeks 1 through 8 had plateaued by week 4, suggesting the treatment period was of a sufficient duration to determine the greater part of the treatment effects of FF on the endpoints used. The proportion of African American/African patients in this study, a group known to exhibit comparatively worse asthma outcomes compared with other ethnic groups,⁴⁴ was small and might reduce the generalizability of these data in this ethnic group. Approximately one fourth of patients in this study were of Asian descent, and the steroid responsiveness of this population appears to be similar to that of white patients,^{45,46} suggesting that the findings from this study can be generalized in these 2 groups.

The need for therapies such as FF reflects the fact that asthma control remains suboptimal in many persistent asthma patients.^{9,47,48} Adherence is considered to be a major factor in suboptimal asthma control, for which once-daily dosing might present an advantage.⁴⁹ The development of ICSs with a very favorable therapeutic ratio and longer duration of effect may also allay concerns about side effects, which can be a further barrier to adherence. Inclusion of ICS with a LABA in a fixed-dose combination is a further strategy to improve the regular use of ICS.^{50,51}

In conclusion, FF is effective and well tolerated when administered at doses of 100 to 400 μ g once daily in the evening in patients with asthma symptomatic on low-dose ICS therapy. Once-daily FF showed similar efficacy to that of twice-daily FP 250 μ g. Based on the efficacy and tolerability profile observed, the 100- μ g and 200- μ g once-daily doses of FF are considered the most appropriate for this patient population for future evaluation either as monotherapy or in combination with a once-daily LABA.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.anai.2012.08.017>.

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eSupplement 1*Key exclusion criteria*

Patients were excluded from study entry if they had any history of life-threatening asthma, respiratory infection, or asthma exacerbation requiring oral corticosteroids within 3 months or hospitalization for asthma within 6 months of study visit 1. Patients were also excluded if they were a current smoker, if they had a smoking history of ≥ 10 pack years, or if they had used tobacco products within the past year. Other exclusion criteria included a history or current evidence of any clinically significant uncontrolled disease, evidence of oral candidiasis, or any history of an adverse reaction to corticosteroids, β_2 agonists, or sympathomimetic drugs. The use of immunosuppressive medications during the study period was not permitted, and patients also were excluded if they had used systemic, oral, or depot corticosteroids within 12

weeks or potent cytochrome P450 3A4 inhibitors (eg, ritonavir, ketoconazole) within 4 weeks of visit 1. Female patients of childbearing potential had to be nonpregnant and using an acceptable method of contraception.

eSupplement 2*Other prohibited medications*

There was to be no use from within 12 weeks of visit 1 of systemic, oral, parenteral, or depot corticosteroids or anti-IgE agents, from within 4 weeks of inhibitors of CYP3A4, or from within 1 week of anti-leukotrienes, combination inhaled β_2 agonist/ICS treatments, or oral or inhaled long-acting β_2 -agonists (LABAs). The use of theophyllines, slow-release bronchodilators, anticholinergics, ketotifen, nedocromil sodium, and sodium cromoglycate were also prohibited from visit 1 onward.

eTable 1

Statistical analysis of change from baseline in AM and PM PEF vs placebo

	FF				FP
	100 μ g OD (N = 105)	200 μ g OD (N = 101)	300 μ g OD (N = 103)	400 μ g OD (N = 99)	250 μ g BD (N = 100)
PM PEF (L/min)					
Difference vs placebo					
LS mean difference	11.9	17.6	17.9	23.8	21.0
95% CI	2.0, 21.8	7.6, 27.6	7.9, 27.8	13.7, 33.8	10.9, 31.0
P value	.018	<.001	<.001	<.001	<.001
AM PEF (L/min)					
Difference vs placebo					
LS mean difference	20.2	20.6	30.1	30.7	29.7
95% CI	9.6, 30.8	10.0, 31.3	19.5, 40.8	19.9, 41.4	19.0, 40.5
P value	<.001	<.001	<.001	<.001	<.001

Abbreviations: BD, twice daily; CI, confidence interval; FF, fluticasone furoate; FP, fluticasone propionate; LS, least squares; OD, once daily; PEF, peak expiratory flow.

eTable 2

Statistical analysis of change from baseline in symptom-free and rescue-free 24-hour periods vs placebo

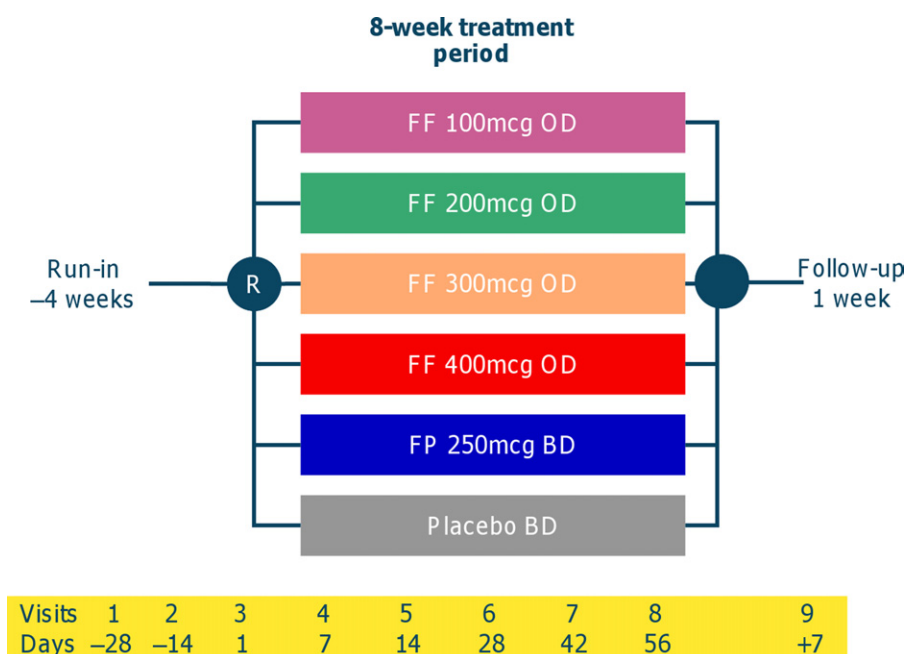
	FF				FP
	100 μ g OD (N = 105)	200 μ g OD (N = 101)	300 μ g OD (N = 103)	400 μ g OD (N = 99)	250 μ g BD (N = 100)
Symptom-free 24-hour periods					
Difference vs placebo					
LS mean difference	4.2	2.2	6.9	10.8	13.2
95% CI	−4.0, 12.4	−6.0, 10.4	−1.2, 15.1	2.6, 19.1	5.0, 21.5
P value	.311	.592	.097	.01	.002
Rescue-free 24-hour periods					
Difference vs placebo					
LS mean difference	9.4	8.2	9.4	8.8	18.9
95% CI	0.9, 17.8	−0.4, 16.7	0.9, 17.9	0.2, 17.3	10.3, 27.5
P value	.030	.060	.031	.045	<.001

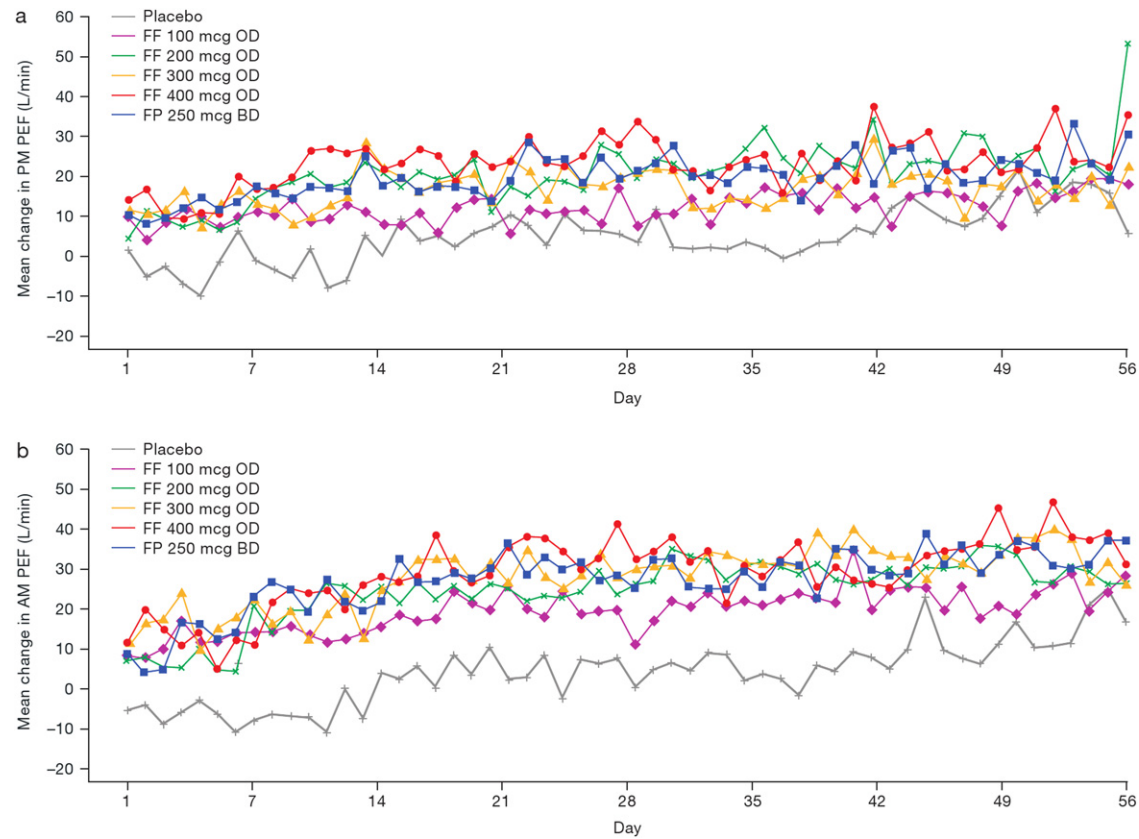
Abbreviations: BD, twice daily; CI, confidence interval; FF, fluticasone furoate; FP, fluticasone propionate; LS, least squares; OD, once daily.

eTable 3
Summary of adverse events (ITT population)

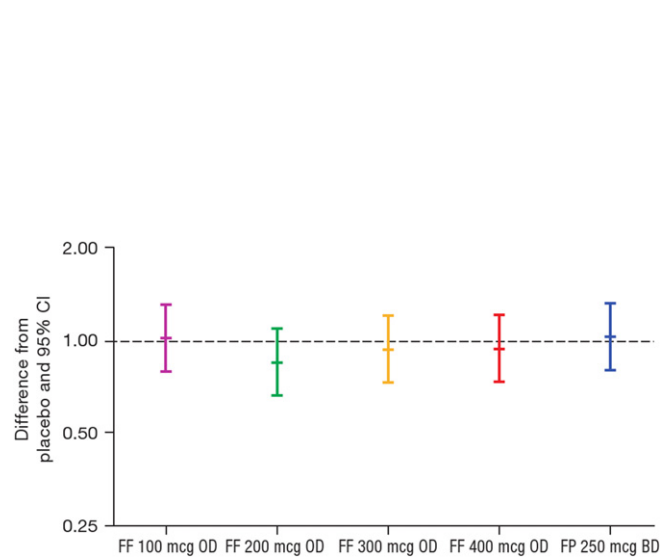
	Placebo (N = 107)	FF				FP
		100 µg OD (N = 105)	200 µg OD (N = 101)	300 µg OD (N = 103)	400 µg OD (N = 99)	250 µg BD (N = 100)
Patients with any on-treatment AE, n (%)	32 (30)	43 (41)	33 (33)	41 (40)	35 (35)	42 (42)
Most common on-treatment AE ($\geq 3\%$ in any treatment group), n (%)						
Headache	6 (6)	9 (9)	8 (8)	8 (8)	9 (9)	8 (8)
Nasopharyngitis	8 (7)	9 (9)	5 (5)	7 (7)	4 (4)	7 (7)
Upper respiratory tract infection	3 (3)	2 (2)	3 (3)	1 (<1)	0	6 (6)
Oral candidiasis ^a	0	3 (3)	1 (<1)	4 (4)	3 (3)	4 (4)
Cough	1 (<1)	2 (2)	0	2 (2)	4 (4)	2 (2)
Back pain	0	1 (<1)	1 (<1)	3 (3)	3 (3)	2 (2)
Dysphonia	1 (<1)	1 (<1)	0	2 (2)	2 (2)	4 (4)
Oropharyngeal pain	0	2 (2)	1 (<1)	1 (<1)	3 (3)	3 (3)
Hypertension	2 (2)	0	3 (3)	2 (2)	2 (2)	0
Diarrhea	0	4 (4)	1 (<1)	1 (<1)	1 (1)	1 (1)
Pain in extremity	3 (3)	1 (<1)	1 (<1)	0	2 (2)	1 (1)
Abdominal pain upper	0	2 (2)	1 (<1)	1 (<1)	3 (3)	0
Sinusitis	1 (<1)	2 (2)	0	0	1 (1)	3 (3)
Abdominal pain	0	3 (3)	1 (<1)	0	1 (1)	1 (1)
Rhinitis	3 (3)	0	2 (2)	1 (<1)	0	0
Pharyngitis	1 (<1)	1 (<1)	0	3 (3)	0	0
Toothache	0	1 (<1)	1 (<1)	0	0	3 (3)
Patients with treatment-related AE, n (%)	1 (<1)	8 (8)	7 (7)	11 (11)	6 (6)	11 (11)
Patients with on-treatment serious AEs, n (%)	0	0	0	1 (<1)	1 (1)	0
Patients with AEs leading to withdrawal, n (%)	0	3 (3)	1 (<1)	0	2 (2)	1 (1)

Abbreviations: AE, adverse event; BD, twice daily; FF, fluticasone furoate; FP, fluticasone propionate; IT, intent-to-treat; OD, once daily.

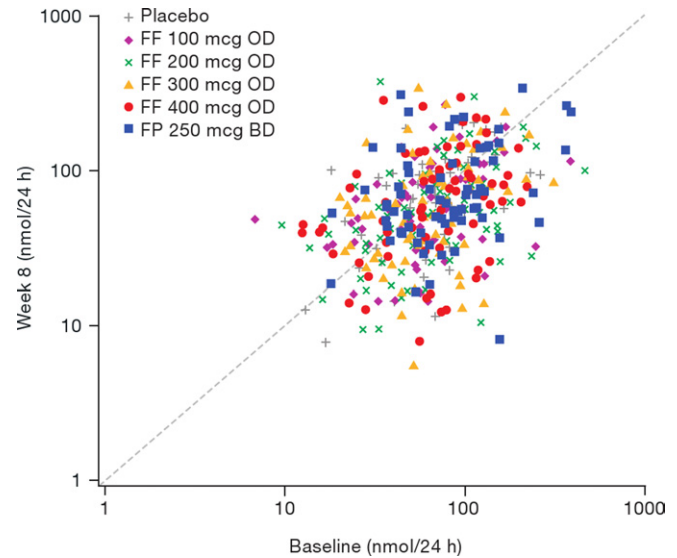
^aIncludes one patient in the FF 300 µg OD group and one patient in the FP 250 µg BD group who were diagnosed as having oral candidiasis, but coded as 'oropharyngeal candidiasis.'**eFigure 1.** Study design. BD, twice daily; FF, fluticasone furoate; FP, fluticasone propionate; OD, once daily.



eFigure 2. Mean change from baseline in daily evening (A) and morning (B) PEF (ITT population). BD, twice daily; FF, fluticasone furoate; FP, fluticasone propionate; OD, once daily; PEF, peak expiratory flow.



eFigure 3. Adjusted treatment ratios and corresponding 95% confidence intervals (CI) for 24-hour urinary cortisol excretion (urinary cortisol population). BD, twice daily; FF, fluticasone furoate; FP, fluticasone propionate; OD, once daily.



eFigure 4. Individual patient urinary cortisol values at baseline and at week 8 (urinary cortisol population). BD, twice daily; FF, fluticasone furoate; FP, fluticasone propionate; OD, once daily.