

Long-term treatment with fluticasone propionate/salmeterol via Diskus improves asthma control versus fluticasone propionate alone

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ABSTRACT

This 52-week study was designed to assess the safety and efficacy of fluticasone propionate/salmeterol combination (FSC) 250/50 micrograms versus fluticasone propionate (FP) 250 micrograms in subjects with persistent asthma symptomatic on open-label FP 100 micrograms. The primary objective of this study was to show that FSC 250/50 micrograms was superior to FP 250 micrograms at increasing pulmonary function as measured by forced expiratory volume in 1 second over a 52-week treatment period. A secondary objective was to compare the rate of asthma attacks defined as (1) a sustained 2-day decrease in morning peak expiratory flow or increase in albuterol use for 2 consecutive days, (2) an asthma exacerbation requiring systemic corticosteroids, or (3) an unscheduled clinic or hospital visit for acute asthma symptoms. Three hundred six subjects received FSC 250/50 micrograms and 315 subjects received FP 250 micrograms. Both treatments were administered twice daily. Treatment with FSC 250/50 micrograms resulted in a significant improvement in lung function compared with FP 250 micrograms ($p < 0.001$). Additionally, treatment with FSC 250/50 micrograms resulted in a reduction in the rate of exacerbations of asthma (i.e., requiring systemic corticosteroids or unscheduled urgent care intervention) compared with FP 250 micrograms (0.170 versus 0.273, respectively; $p = 0.017$). There was no differentiation between treatments for less severe attacks of asthma. FSC 250/50 micrograms showed consistently greater improvement in lung function, symptom control, and decreased albuterol use. In addition, FSC 250/50 micrograms-treated subjects experienced fewer severe asthma exacerbations than subjects treated with FP 250 micrograms.

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Asthma is a chronic inflammatory disease of the airways characterized by variable airflow obstruction secondary to airway inflammation and smooth muscle dysfunction. Therapeutic decisions for the treatment of asthma are guided by the severity of disease and level of control, both defined by patient's symptoms, risk factors, and objective measurements of airflow. To achieve optimal asthma control, a stepwise approach to therapy is recommended by national and international guidelines that outline a plan for the titration of a medication or combinations of medications to match the individual's level of asthma severity and control. Despite guideline-directed therapy, many patients with asthma remain uncontrolled (Fuhlbrigge; AAP 2009).

Clinical studies¹ of 3–6 months duration investigating treatment with a low-dose inhaled corticosteroid (ICS) and long-acting β_2 -agonist (LABA) have indicated greater efficacy than higher doses of ICS in improving overall asthma control, airflow obstruction, and reducing asthma exacerbations while maintaining a similar safety profile.^{2–5} Likewise, results from a 12-month study comparing asthma control in symptomatic subjects with mild-to-moderate persistent asthma treated with ICS and LABA combination or ICS alone showed that significantly fewer subjects in the ICS and LABA combination treatment arm required an increase in study medication to achieve effective control and had significantly fewer exacerbations while maintaining a similar safety profile.⁶ Additionally, retrospective observational studies have shown decreases in asthma exacerbations in patients receiving ICS and LABA therapy compared with ICS therapy alone.^{7–8}

The present study was designed to provide additional efficacy and safety data regarding the long-term risk/benefit of fluticasone propionate/salmeterol (FSC) when compared with an equivalent dose of an ICS in subjects symptomatic on an ICS-containing regimen. Specifically, this study investigated the benefits of the addition of an LABA to a medium-dose steroid (FSC Diskus

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250/50 μg) when compared with treatment with a medium-dose steroid (fluticasone propionate [FP] Diskus 250 μg) in subjects who remained symptomatic despite treatment with a low-dose steroid (FP Diskus 100 μg) given during the run-in period. Although pulmonary function was the primary efficacy variable in this study, the rate of asthma attacks, an exploratory term, was assessed as a secondary objective. Most efficacy studies have traditionally focused on end points that evaluate the impairment domain. Evaluation of the risk domain requires longer-term treatment to assess less frequent asthma exacerbations. This study attempted to explore the study-defined term "asthma attack" to help define the risk of acute decline in asthma status.

METHODS

Subject Selection

Male or female subjects, ≥ 12 years of age, with a clinical diagnosis of asthma, defined by the American Thoracic Society,⁹ for ≥ 6 months before screening were eligible for inclusion in this study. Subjects were required to have a prebronchodilator forced expiratory volume in 1 second (FEV_1) of 50–85% of predicted normal. In addition, subjects had to show an FEV_1 reversibility of $\geq 12\%$ after 2–4 puffs of albuterol at visit 1. Eligible subjects were required to have treatment with a low-to-medium dose of ICS or combination ICS/LABA controller medications if the ICS was a low dose for ≥ 4 weeks before screening. Additionally, eligible subjects must have reported being symptomatic while taking their controller medication in the 4 weeks before screening.

Exclusion criteria included life-threatening asthma in the 12 months before screening, seasonal or exercise-induced asthma without other manifestations of persistent asthma, or had concurrent respiratory disease or any other significant concurrent condition/disease. Subjects were excluded if they had worsening asthma in the 4 weeks before screening including an emergency room visit, hospitalization, or use of oral/parenteral corticosteroids. Concurrent use of medications that could have affected the course of asthma or interacted with study medication was prohibited.

Study Design

This study (ADA109055) was a 52-week, international, multicenter, randomized, double-blind, parallel-group study designed to compare the improvement in lung function (FEV_1) achieved in adults and adolescents treated with FSC (Advair/Seretide/Viani; GlaxoSmithKline, Research Triangle Park, NC) or FP (Flovent/Flixotide; GlaxoSmithKline) alone over the 52-week treatment period. Subjects from Argentina, Brazil, United

States, Canada, and the Philippines participated in this study.

Eligible subjects entered the 14- to 21-day run-in period. During run-in, subjects received open-label FP 100 μg twice daily (b.i.d.). After 14 days of the run-in period telephone contact to the subject was made to assess subject's symptoms, compliance, and safety. Those who were symptomatic during the last 7 days of the run-in period were randomized to receive FSC 250/50 μg or FP 250 μg b.i.d. The randomization criteria consisted of an asthma symptom score of at least 1 (1 = symptoms for one short period during the previous 24 hours) on ≥ 2 or more days and recorded use of albuterol inhalation aerosol on any 2 or more days during the 7 consecutive days immediately before the randomization visit.

Throughout the run-in and double-blind treatment periods of the study, subjects entered into a diary the following: morning peak expiratory flow (A.M. PEF), 24-hour albuterol use, 24-hour asthma symptom score (using a 6-point scale), and productivity scores. Diary information was used to assess eligibility for randomization.

The final study protocol and informed consent documentation were approved by institutional review boards and/or independent ethics committees at each participating site and written informed consent was obtained from all subjects before any study-specific procedures. For subjects < 18 years of age, written informed consent was obtained from a parent and/or legal guardian. The study was performed in accordance with the Declaration of Helsinki and in compliance with International Conference on Harmonization Good Clinical Practice guidelines (ClinicalTrials.gov identifier: NCT00452699).

Efficacy and Safety Assessments

Spirometry was conducted on a monthly basis using the sites spirometry equipment, which met or exceeded American Thoracic Society recommendations. FEV_1 percent predicted normal values were based on the National Health and Nutrition Examination Survey III predicted normal values.¹⁰ The primary measure of efficacy was trough, predose FEV_1 change from baseline over the 52-week treatment period. Secondary measures of efficacy included A.M. PEF (measured daily throughout the study with the use of an electronic handheld peak flow meter), percentage of symptom-free days, and rate of asthma attacks per subject per year. The related efficacy measure of percentage of symptom-free days was percentage of rescue-free days. Related efficacy measures of the rate of asthma attacks were the probability of not being withdrawn from the study (survival) per protocol-defined asthma withdrawal criteria and the rate of asthma exacerbations.

tions. Subjects with asthma attacks or exacerbations were not required to withdraw but were allowed to continue in the protocol, unless two or three asthma exacerbations occurred in a 24- or 52-week period, respectively. Safety was assessed through monitoring of adverse events from the time of subject consent to the end of follow-up period.

Data Analysis and Statistical Methods

Statistical analyses were performed using SAS Version 9.1 software (SAS Inc., Cary, NC) in a UNIX reporting environment. Using a two-sample two-sided *t*-test with an SD estimate of 0.37 L for trough, predose FEV₁ change from baseline, 289 subjects per treatment group were needed to detect a significant difference of 0.10 L between treatment groups at the 0.05 significance level with 90% power. The analysis population was the ITT population, which included all subjects randomized to study drug. The target enrollment of ~600 randomized subjects allowed for a 5% attrition rate because of early discontinuations from the study. Statistical tests of all efficacy measures were two-sided alternative hypothesis tests conducted at the 0.05 significance level. A hierarchical testing procedure to control type I error for multiplicity was used for the treatment comparisons of efficacy end points. The Hochberg method was also used to control the overall type I error rate across the secondary efficacy measures.¹¹

The primary efficacy measure (mean change from baseline in predose FEV₁ over the 52-week treatment period) was compared between treatment groups using analysis of covariance (ANCOVA) including terms for treatment group, pooled investigator (geographic combination of sites), and baseline predose FEV₁ in the model. Secondary measures of efficacy were A.M. PEF, percentage of symptom-free days, and rate of asthma attacks. The related efficacy measure of percentage of symptom-free days was percentage of rescue-free days. The related efficacy measure of rate of asthma attacks was the probability of not being withdrawn from the study (survival) per protocol-defined asthma withdrawal criteria and the rate of asthma exacerbations. The analysis plan to manage multiplicity defined that the related efficacy measures nested under asthma attacks would be analyzed using descriptive statistics, but not considered for statistical comparison, if the asthma attack measure was determined not statistically significant.

The A.M. PEF, percentage of symptom-free days, and percentage of rescue-free days were compared between treatment groups using ANCOVA. Baseline for each of the diary measures was defined as the mean of the diary scores recorded over the 7 days immediately before the randomization visit (visit 2).

The definition of asthma attack was formulated for this study and was defined to capture both mild loss of asthma control and more severe episodes or worsening asthma. The criteria that defined an asthma attack during the double-blind treatment period were a $\geq 20\%$ decrease in A.M. PEF from baseline on any 2 consecutive days; a $\geq 70\%$ increase in albuterol use from baseline on any 2 consecutive days; the occurrence of an asthma exacerbation defined as the requirement for treatment with an oral or parenteral corticosteroid, or an unscheduled urgent care visit (e.g., unscheduled clinic visit, physician office visit, emergency room visit, or hospitalization) for acute asthma symptoms requiring intervention. The analysis of asthma attacks compared the rate of asthma attacks per subject per year between treatment groups using a negative binomial regression model. The model included terms for treatment group, pooled investigator, and baseline severity (baseline FEV₁ percent predicted), with log (time of treatment) as an offset variable. The probability of not being withdrawn (survival) per protocol-defined asthma criteria, as well as time to first exacerbation, was summarized with Kaplan-Meier estimates and compared between treatment groups using a Cox proportional hazards model. The rate of asthma exacerbations was analyzed in the same manner as rate of asthma attacks.

RESULTS

Study Subjects

A total of 937 subjects were screened; 621 subjects were randomized to treatment and were included in the ITT population for analysis: 306 to FSC 250/50 μg and 315 to FP 250 μg . During the 52-week treatment period 81 (26%) subjects treated with FSC 250/50 μg and 73 (23%) subjects from the FP 250 μg withdrew. The primary reasons for withdrawal were similar between treatment groups (Fig. 1). Screening demographics and asthma characteristics, including sex, race, age, asthma duration, and pulmonary function, were well matched between treatment groups (Table 1). The median exposure to double-blind study drug was 364 days and mean treatment compliance, as derived from the Diskus dose counter, was $>93\%$ in both treatment groups¹² (Table 1).

Pulmonary Function

All subjects received open-label FP 100 μg during the run-in period. Treatment with open-label FP 100 μg significantly improved the mean percent predicted FEV₁ from screening to the baseline visit ($5.2 \pm 0.64\%$ and $4.0 \pm 0.58\%$) in subjects subsequently randomized to FSC 250/50 μg and FP 250 μg , respectively (Fig. 2). Study population *post hoc* analysis conducted to compare pulmonary function at screening and baseline

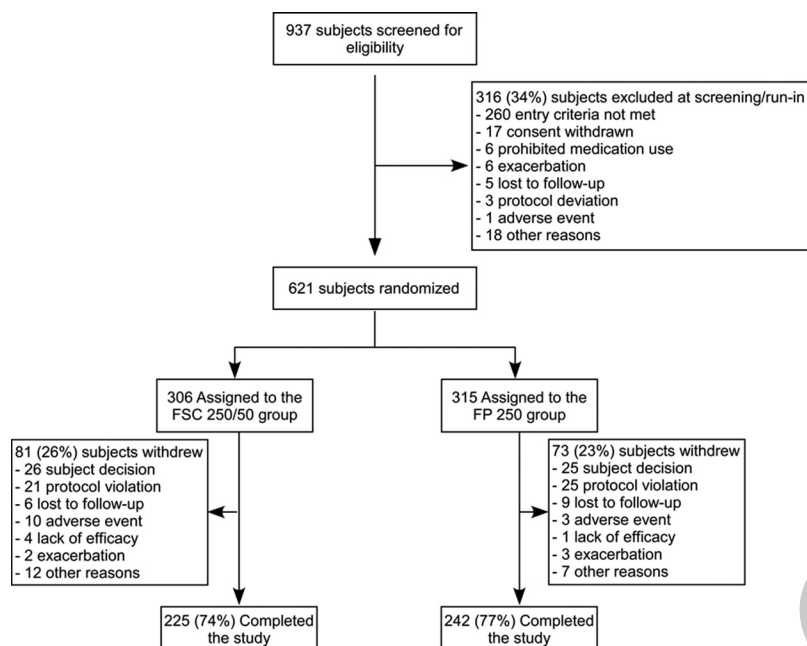


Figure 1. Study flow diagram.

Table 1 Intent-to-treat population demographics and pulmonary function at screening

	FSC 250/50 μg (n = 306)	FP 250 μg (n = 315)
Mean age, yr (SD)	36.8 (15.52)	39.3 (15.52)
Sex, F/M %	62/38	64/36
Race, %		
White	64	66
Black	21	19
Asian	13	13
Other	2	2
Subjects with duration of asthma ≥ 15 yr, %	49	61
History of atopy, n (%)	181 (60)	194 (62)
Mean % reversibility (SD)	22.3 (10.91)	21.0 (9.00)
Mean prebronchodilator FEV ₁ , L (SD)	2.19 (0.62)	2.18 (0.60)
Mean postbronchodilator FEV ₁ , L (SD)	2.68 (0.79)	2.62 (0.70)
Mean prebronchodilator FEV ₁ , % predicted (SD)	68.9 (9.90)	69.0 (9.57)
Previous medication use,* % of treatment arm		
Short-acting β_2 -agonists	86	88
Fluticasone propionate/salmeterol combination	39	41
Budesonide	24	19
Fluticasone propionate	13	14
Beclomethasone dipropionate	8	6
Budesonide/formoterol combination	6	7
Mometasone furoate	5	6
Double-blind study drug exposure		
Median exposure (days)	364.0	364.0
Mean % compliance (SD)	93.7 (17.49)	95.0 (15.04)

*Reported use of asthma medications in the 30 days before screening, use of other controller medications was reported $< 5\%$. FEV₁ = forced expiratory volume in 1 s; FP = fluticasone propionate; FSC = fluticasone propionate/salmeterol combination.

determined that 20% of the ITT population (21% of those randomized to the FSC 250/50 μg and 18% of those randomized to the FP 250 μg) had a baseline

percent predicted $> 85\%$ at baseline (above the screening criteria of 85% predicted; Table 2). Although lung function improved in a subset during run-in, all

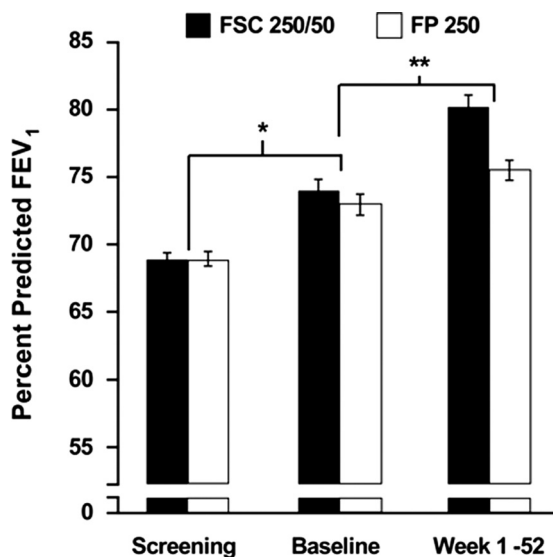


Figure 2. Mean percent predicted forced expiratory volume in 1 second (FEV₁) at screening, baseline, and end of study. Results reflect the treatment groups assigned at baseline and indicate a significant increase (*) in percent predicted FEV₁ between screening and baseline (paired t-tests, $p < 0.001$). A significant difference (**) was also observed with a treatment group comparison between baseline and end of study (weeks 1–52; analysis of covariance [ANCOVA], $p < 0.001$).

subjects randomized to double-blind therapy remained symptomatic, as required by study randomization criteria.

Predose FEV₁ values were similar between treatment groups (Table 3). Over the 52-week double-blind treatment period a statistically significant greater mean increase from baseline in predose FEV₁ and percent predicted FEV₁ was observed for FSC 250/50 μ g compared with FP 250 μ g (0.09 L; Table 4 and Fig. 2). From baseline to end of study, treatment group changes in mean percent predicted FEV₁ were $6.16 \pm 0.49\%$ and $2.72 \pm 0.44\%$ for FSC 250/50 μ g and FP 250 μ g, respectively.

Baseline mean A.M. PEF was similar between the treatment groups (Table 3). Over the 52-week treatment period, a greater mean increase from baseline in A.M. PEF was observed for FSC 250/50 μ g (23.6 L/min) compared with the FP 250 μ g (9.8 L/min) and the adjusted mean difference was statistically significant (Table 4; $p < 0.001$).

Symptom-Free and Rescue-Free Days

The baseline mean percentage of symptom-free and percentage of rescue-free days were similar between the treatment groups (Table 3). Over the 52-week treatment period, a greater mean increase in the percentage of symptom-free days was observed for FSC 250/50 μ g (37.1%) compared with FP 250 μ g (28.5%) and the adjusted mean difference was statistically significant ($p < 0.001$). There was also a significantly greater mean

increase in the percentage of rescue-free days for FSC 250/50 μ g (38.6%) compared with FP 250 μ g (29.4%) and the adjusted mean difference was statistically significant ($p < 0.001$).

Asthma Attacks

During the double-blind treatment period asthma attacks were experienced by 58% of the FSC 250/50 μ g and 66% of the FP 250 μ g subjects. The majority of the asthma attacks (71% in the FSC 250/50 μ g and 67% in the FP 250 μ g) met the A.M. PEF defined criteria (a sustained 2-day decrease in A.M. PEF), approximately one-third met the albuterol criteria (increase in albuterol use for 2 consecutive days), and few asthma attacks were related to the occurrence of an asthma exacerbation (Fig. 3 A). Asthma attacks could have been a result of one or more of these criteria. Overall, the mean asthma attack rate (per subject per year) was lower in the FSC 250/50 μ g than in the FP 250 μ g subjects; however, this result was not statistically significant (Fig. 3 B).

A *post hoc* analysis was conducted to determine which of the asthma attack criterion contributed to the lack of significant difference between treatment arms for the asthma attack rate. The analysis of the A.M. PEF criterion, and albuterol use criterion, indicated that there was a similar rate between the treatment arms. However, the analysis of exacerbations requiring systemic corticosteroids or an urgent care intervention showed a nominally significant difference between treatment arms with an asthma exacerbation rate for the FSC 250/50 μ g of 0.170 compared with 0.273 for the FP 250 μ g ($p = 0.017$; Fig. 3 C).

Exacerbations

Severe exacerbations of asthma (defined as requiring oral or parenteral corticosteroid, hospitalization for asthma, or an unscheduled urgent care for acute asthma symptoms requiring intervention) were experienced by a lower number and percentage of subjects receiving FSC 250/50 μ g ($n = 49$; 12%) versus FP 250 μ g ($n = 83$; 23%). The mean asthma exacerbation rate was lower for FSC 250/50 μ g compared with FP 250 μ g (treatment comparison ratio = 0.625; $p = 0.017$).

The time to first exacerbation was also examined in a *post hoc* analysis. Time to first exacerbation was significantly delayed in subjects treated with FSC 250/50 μ g compared with FP subjects treated with 250 μ g, with a hazard ratio of 0.525, corresponding to a risk reduction of 47.5% (Fig. 4 A; 95% CI, 0.352–0.782; $p = 0.002$). Additionally, analysis indicated that there was less reduction in the mean change from baseline in A.M. PEF (L/min) pre- and postexacerbation in the FSC 250/50 μ g group when compared with the FP 250 μ g group (Fig. 4 B).

Table 2 Screening and baseline pulmonary function tests by baseline percent predicted (ADA109055, intent-to-treat population)

	>85% Predicted at Baseline*			≤85% Predicted at Baseline*		
	FSC 250/50 µg (n = 65)	FP 250 µg (n = 57)	Total (n = 122)	FSC 250/50 µg (n = 241)	FP 250 µg (n = 258)	Total (n = 499)
Screening						
Prebronchodilator FEV ₁ (L) mean (SD)	2.43 (0.57)	2.35 (0.61)	2.39 (0.59)	2.13 (0.62)	2.14 (0.59)	2.13 (0.60)
Percent predicted FEV ₁ (%)# mean (SD)	76.3 (7.25)	78.2 (6.56)	77.2 (6.97)	66.9 (9.57)	66.9 (8.92)	66.9 (9.23)
Postbronchodilator FEV ₁ (L) mean (SD)	3.07 (0.79)	2.90 (0.75)	2.99 (0.77)	2.58 (0.76)	2.56 (0.68)	2.57 (0.72)
FEV ₁ Reversibility (%) mean (SD)	26.2 (12.8)	24.2 (10.2)	25.3 (11.7)	21.2 (10.1)	20.3 (8.6)	20.8 (9.4)
Baseline*						
Percent predicted FEV ₁ (%)# mean (SD)	94.8 (8.08)	93.4 (7.48)	94.1 (7.81)	68.4 (10.9)	68.5 (10.5)	68.5 (10.7)

*Randomization visit.

#Prebronchodilator value.

FEV₁ = forced expiratory volume in 1 s; FP = fluticasone propionate; FSC = fluticasone propionate/salmeterol combination.

Table 3 Intent-to-treat population pulmonary function and asthma characteristics at baseline*

	FSC 250/50 µg (n = 306)	FP 250 µg (n = 315)
Prebronchodilator FEV ₁ , L (SE)	2.36 (0.04)	2.30 (0.04)
Prebronchodilator FEV ₁ , % predicted (SE)	74.0 (15.0)	73.0 (13.9)
A.M. PEF, L/min (SE)	362.3 (6.52)	366.1 (6.47)
Symptom-free days (%)	20.8 (1.41)	19.7 (1.45)
Rescue-free days (%)	20.0 (1.53)	19.0 (1.45)

*Randomization visit (end of run-in period).

A.M. PEF = morning peak expiratory flow; FEV₁ = forced expiratory volume in 1 s; FP = fluticasone propionate; FSC = fluticasone propionate/salmeterol combination.

Health Outcomes Assessments

Baseline Asthma Control Test (ACT, QualityMetric, Inc., Lincoln, RI) scores were determined at the randomization visit and the end point value was determined from the last questionnaire collected (Fig. 5). The baseline mean total ACT scores were similar between treatment groups (FSC = 15.8; FP = 16), suggesting that asthma was not well controlled at baseline. At end point, a statistically significant greater increase from baseline in the mean total ACT score was observed for FSC 250/50 µg (mean change = 4.5) compared with the FP 250 µg subjects (mean change = 3.5). Greater increases from baseline were also observed in mean total ACT scores in the FSC 250/50 µg group than in the FP 250 µg group at every clinic visit and the adjusted mean differences were statistically significant at most (10/14) visits.

Safety Assessments

Over the 52-week treatment period, fewer subjects treated with FSC 250/50 µg had at least one physician office visit because of an asthma exacerbation (29 subjects, 9%) compared with FP 250 µg (51 subjects, 16%). The incidence of urgent care visits or emergency department visits for asthma exacerbations was ≤2% in each treatment group. Few subjects were hospitalized due to asthma exacerbation (three subjects in the FSC 250/50 µg and no subjects treated with FP 250 µg). For those subjects who were hospitalized, the median length of stay was 3 days and all events resolved. The most commonly reported cause of asthma exacerbation, as identified by study investigators, was upper respiratory tract infections.

The incidence of drug-related adverse events was similar between treatment groups. Oral candidiasis

Table 4 End of study (wk 52) pulmonary function and asthma characteristics

	FSC 250/50 μg (n= 306)	FP 250 μg (n= 315)
Baseline FEV ₁ , L (SE)*	2.36 (0.042)	2.30 (0.04)
Mean change from baseline (SE)	0.20 (0.017)	0.09 (0.015)
p Value	<0.001	
Percent predicted FEV ₁ (%) mean (SE)*	81.2 (1.17)	75.9 (0.99)
A.M. PEF (SE)	385.5 (6.53)	375.8 (6.28)
Mean change from baseline	23.6 (2.47)	9.8 (2.40)
p Value	<0.001	
Percent symptom-free days (SE)*	58.0 (2.00)	47.9 (1.96)
Mean change from baseline	37.1 (2.02)	28.5 (1.90)
p Value	<0.001	
Percent albuterol-free days (SE)*	58.6 (2.00)	48.2 (1.98)
Mean change from baseline	38.6 (2.06)	29.4 (1.80)
p Value	<0.001	

*Calculated as the number of symptom or rescue-free days divided by the total number of days in the treatment period $\times 100$. A.M. PEF = morning peak expiratory flow; FEV₁ = forced expiratory volume in 1 s; FP = fluticasone propionate; FSC = fluticasone propionate/salmeterol combination.

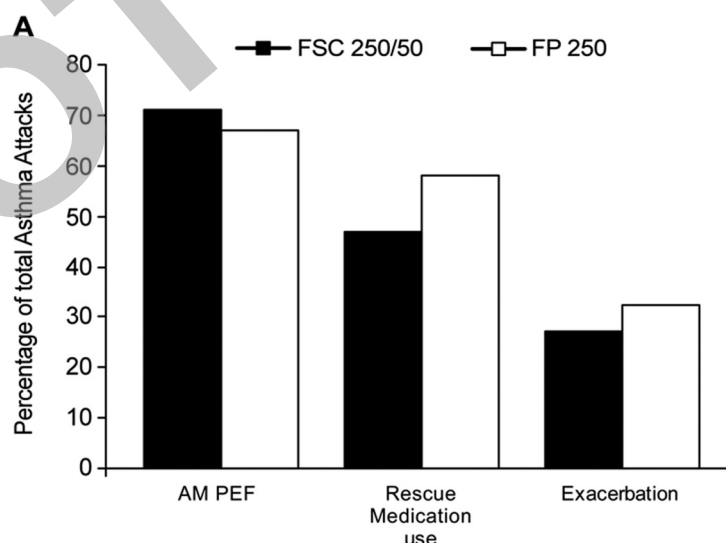
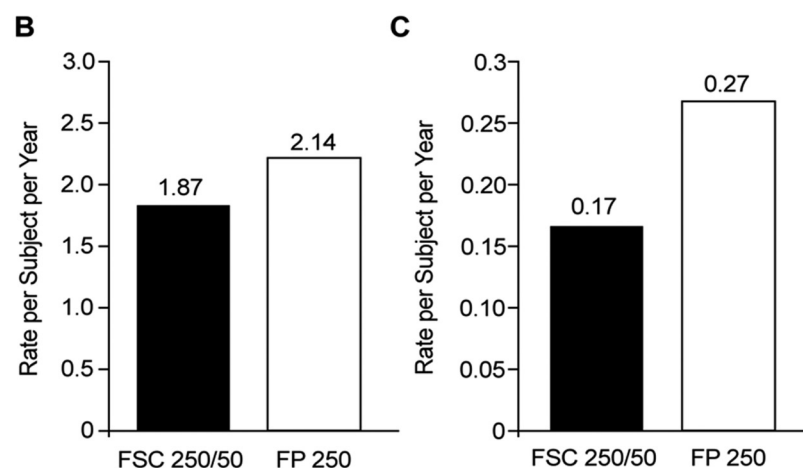


Figure 3. Asthma attacks. (A) The contribution of each of the asthma attack criteria to the percentage of total asthma attacks that occurred during the study. More than one criterion could have been met for each individual attack. (B) Lower mean annual asthma attack rate (per subject per year) in the fluticasone propionate/salmeterol combination (FSC) 250/50 μg treatment group in comparison with the fluticasone propionate (FP) 250 μg group (treatment comparison ratio = 0.874; 95% CI [0.708, 1.080]; $p = 0.212$). (C) Lower mean annual exacerbation rate (per subject per year) in the FSC 250/50 μg treatment group in comparison with the FP 250 μg group (treatment comparison ratio = 0.623; 95% CI [0.423, 0.918]; $p = 0.017$).



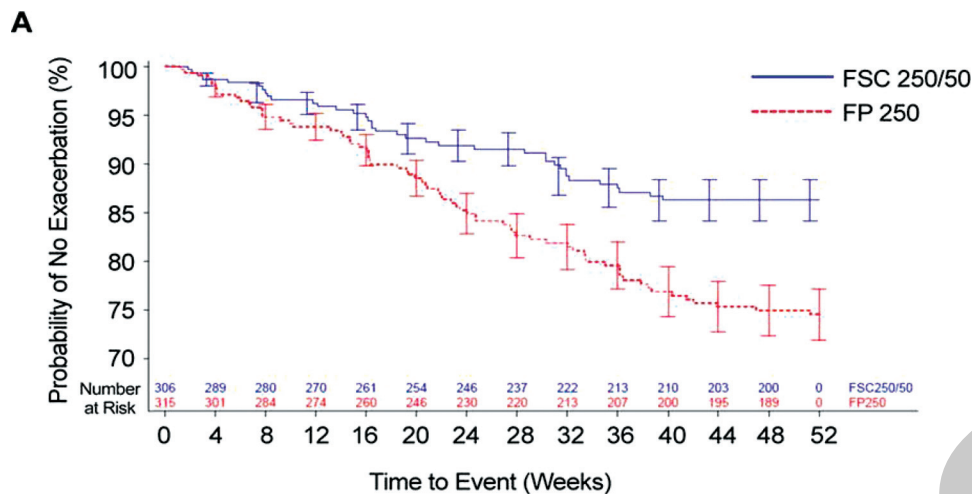


Figure 4. Asthma exacerbations. (A) Probability of having no exacerbations during the double-blind treatment period as determined by Kaplan-Meier estimates. Results represent a delay in the time to first exacerbation as determined by post hoc analysis in subjects treated with fluticasone propionate/salmeterol combination (FSC) 250/50 μg compared with fluticasone propionate (FP) 250 μg , with a hazard ratio of 0.525 ($p = 0.002$). Solid line represents FSC 250/50 μg and dotted line represents FP 250 μg . (B) Mean change from baseline in daily morning peak expiratory flow (A.M. PEF) in the 7 days before and the 7 days after an asthma exacerbation (FSC 250/50 μg group, $n = 33$; FP 250 μg group, $n = 61$; mean trough A.M. PEF at day 0 for FSC 250/50 μg group = 318.3 L/min and for FP 250 μg group = 311.9 L/min). Asterisks (*) indicate significantly different in mean change from baseline when compared with FP 250 μg ($p < 0.05$).

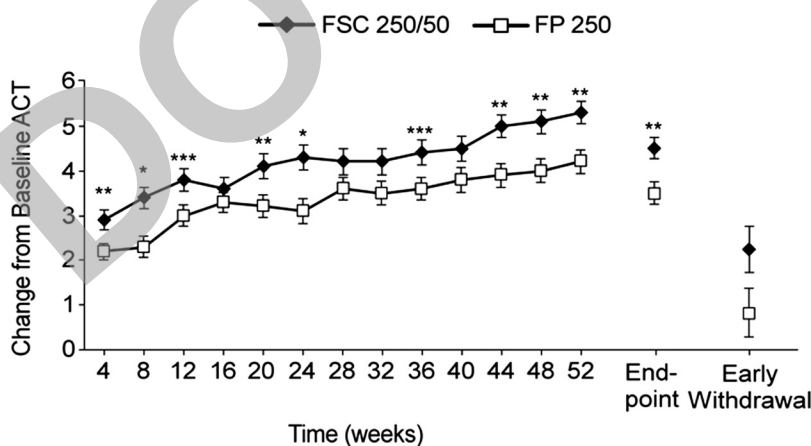
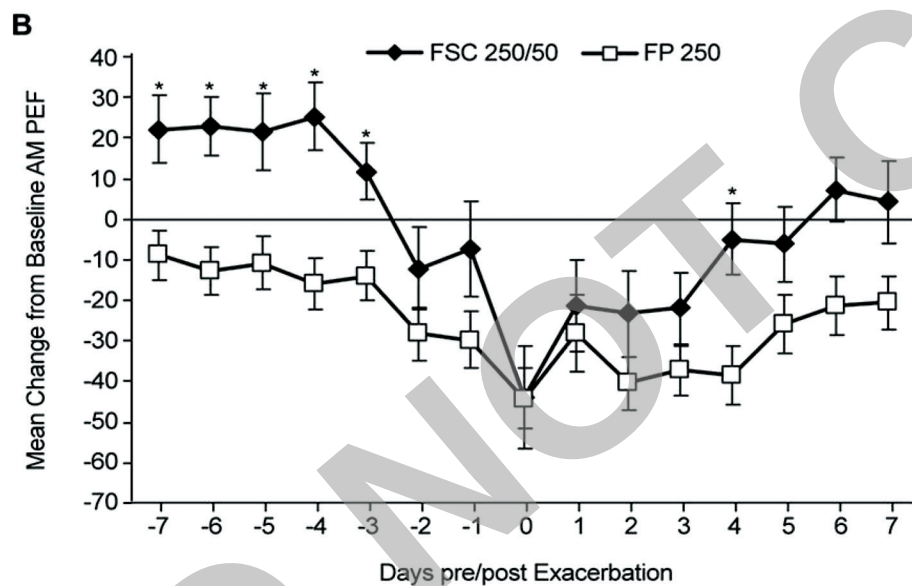


Figure 5. Health outcomes assessments. Change from baseline Asthma Control Test (ACT) scores at each clinic visit throughout the double-blind treatment period. The adjusted mean difference was statistically significant at most visits (10 of 14) and at study end point. Asterisks (*, **, and ***) indicate significantly different mean change from baseline ACT score when compared with FP 250 μg ; * $p < 0.001$; ** $p < 0.01$; and *** $p \leq 0.05$.

was the most frequently reported drug-related adverse event and occurred it with an incidence of 2% in each treatment group. There were 25 subjects with serious adverse events during this 52-week study and there were no deaths in either treatment group. One serious

adverse event occurred during the run-in period (diverticulitis) for a screen failure and 24 subjects experienced serious adverse events postrandomization (14 subjects in the FSC 250/50 μg treatment arm and 10 subjects in the FP 250 μg treatment arm). Serious ad-

verse events that occurred in more than one subject were asthma exacerbation (three in the FSC 250/50 μg group) and pneumonia (two in the FSC 250/50 μg). None of the serious adverse events were considered related to study treatment by the investigators.

DISCUSSION

Randomized clinical studies are primarily 12–24 weeks in duration and indicate that the combination of ICS and LABA is more effective than higher doses of ICS in improving overall asthma control defined as impairment.^{5,13–16} Reducing asthma exacerbations, defined as risk, is noted in results from 52-week trials such as the Gaining Optimal Asthma Control (GOAL) study. Additionally, meta-analyses support the recommendation for combination therapy as the preferred treatment option compared with increasing the ICS dose.^{17–19} The present 52-week study provides further information on the potential longer-term benefits and risks of commonly prescribed asthma regimens in a clinical trial setting. Subjects treated with ICS and LABA combination showed a significant improvement in lung function parameters (FEV_1 and A.M. PEF) and albuterol use and showed a nominal reduction in the rate of severe exacerbations (*i.e.*, exacerbations requiring systemic corticosteroids or unscheduled urgent care intervention).

Combination therapy has also indicated efficacy in subjects not fully controlled with low-to-medium dose ICS.²⁰ In this study subjects on low-to-medium dose ICS or a combination controller medication containing a low-dose ICS, for at least 30 days before screening, were entered into a low-dose treatment (FP 100 μg) run-in period. *Post hoc* analysis showed that there was a statistically significant, and unpredicted, increase in lung function during the run-in period. This increase was unexpected considering that ~40% of the study population reported use of ICS + LABA combination therapy within 30 days before the run-in period, while the majority of the remaining population reported taking low-to-moderate doses of budesonide or FP. These results may have been related to poor patient compliance to asthma medication before the study entry. Consequently, 20% of the subjects randomized to double-blind treatment had a percent predicted FEV_1 at baseline of >85%, above the criteria for entrance, characteristics indicative of mild persistent asthma. These subjects were not the target of this study.²⁰ The study population contained a subset of patients that were milder and less symptomatic than observed in past similarly designed clinical studies.^{2,21–23} Even with these findings, statistically significant superiority of FSC 250/50 μg compared with FP 250 μg was noted for the primary and most of the secondary and related efficacy end points.

There was a numerical but not statistical reduction in “asthma attacks” in the FSC group. This composite definition of “asthma attacks” reflects both impairment (loss of asthma control) and risk (severe asthma exacerbations) domains. The majority of the “asthma attacks” were caused by the impairment criteria (Fig. 3 A). Only a small percent of asthma attacks were classified based on the asthma exacerbation criterion (Fig. 3 A). This suggests that the efficacy measure of worsening asthma may have been inadequate to differentiate a clinically relevant asthma attack and not adequate to allow for differentiation between the two treatment groups. Thus, a composite definition of asthma attacks weighted toward impairment criteria is not a valid measure of “real-life” asthma exacerbations and may capture the normal variability of asthma symptoms. In contrast, there was a numerically greater reduction in the rate of asthma exacerbations per subject per year (defined with more stringent consensus criteria) when FSC 250/50 μg was compared with FP 250 μg (Fig. 3 C), consistent with previous studies.^{2,6}

In conclusion, in this 52-week study, FSC 250/50 μg showed significant improvement in lung function, albuterol use, and asthma symptoms compared with FP 250 μg . Additionally, the safety profile for both treatments was similar. The definition selected for “asthma attacks” as a composite measure of acute decline in asthma status should be weighted more heavily to components of the risk domain, as defined by current asthma guidelines where FSC 250/50 μg showed nominal superiority to FP 250 μg .²⁰

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