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<b>Study No.:</b> ADA109055
<b>Title:</b> A 52-week, Randomized, Double-Blind, Parallel-Group Study of Fluticasone Propionate/Salmeterol DISKUS™ Combination Product (FSC) 250/50mcg BID and Fluticasone Propionate (FP) DISKUS 250 mcg BID in Treatment of Subjects with Asthma
<b>Rationale:</b> This study was conducted to provide information on the efficacy and safety of the long-acting beta agonist (LABA) component of a commonly prescribed asthma treatment regimen. This study evaluated the efficacy of the regular use of FSC DISKUS 250/50 twice daily (BID) compared with FP DISKUS 250 BID in a 52-week study using measures of pulmonary function and asthma control.
<b>Phase:</b> IV
<b>Study Period:</b> 03 May 2007 through 15 May 2009
<b>Study Design:</b> Randomized, double-blind, parallel-group, multicenter study
<b>Centers:</b> A total of 61 centers randomized subjects to treatment: 48 in the United States, 6 in Argentina, 3 in Brazil, 2 in Canada, and 2 in the Philippines.
<b>Indication:</b> Asthma
<b>Treatment:</b> FSC DISKUS 250/50 mcg BID or FP DISKUS 250 mcg BID for 52 weeks
<p><b>Objectives:</b> The primary objective of this study was to demonstrate that FSC DISKUS 250/50 BID is superior to FP DISKUS 250 BID at increasing pulmonary function as measured by forced expiratory volume in one second (FEV<sub>1</sub>) over a 52-week treatment period. Secondary objectives were to compare the efficacy of the two treatment groups with respect to the following parameters: morning (AM) peak expiratory flow (PEF), percent of symptom-free days, and the incidence of asthma attacks.</p> <p>The criteria for worsening asthma that were considered to represent an asthma attack during the double-blind treatment period of the study were defined as follows:</p> <ol style="list-style-type: none"> <li><b>PEF Stability Criteria:</b> A <math>\geq 20\%</math> decrease in AM PEF (from baseline or below the AM PEF Stability Limit) on any 2 consecutive days. The AM PEF Stability Limit was defined as 80% of the baseline AM PEF. Baseline AM PEF was defined as the average of the last 7 days prior to randomization.</li> <li><b>Albuterol Use Criteria:</b> A <math>\geq 70\%</math> increase in albuterol use (from baseline) on any 2 consecutive days (with a minimum of 2 puffs increase). Baseline was defined as the average of the last 7 days prior to randomization.</li> <li><b>Asthma Exacerbation Criteria:</b> Occurrence of an asthma exacerbation, defined as the requirement of treatment with an oral or parenteral corticosteroid OR an unscheduled urgent care (e.g., unscheduled clinic visit, MD office visit, emergency room visit, hospitalization) for acute asthma symptoms requiring intervention.</li> </ol>
<b>Primary Outcome/Efficacy Variable:</b> Mean change from baseline in pre-dose FEV <sub>1</sub> over Weeks 1-52
<b>Secondary Outcome/Efficacy Variable(s):</b> Mean change from baseline in AM PEF over Weeks 1-52, mean change from baseline in the percentage of symptom-free days over Weeks 1-52, and rate of asthma attacks per subject per year.
<b>Statistical Methods:</b> It was estimated that 289 subjects per treatment group would provide approximately 90% power for detection of a significant difference of 0.10 L in trough, pre-dose FEV <sub>1</sub> change from baseline over the 52-week treatment period at a significance level of 0.05 based on a two-sample two-sided t-test with a standard deviation estimate of 0.37L. The analysis

population for this study was the Intent-to-Treat (ITT) Population which included all subjects randomized to study drug.

The primary efficacy measure (change from baseline in pre-dose FEV<sub>1</sub> over the 52-week treatment period) and secondary measures of AM PEF and percentage of symptom-free days were compared between treatment groups using analysis of covariance (ANCOVA). The analysis of asthma attacks compared the rate of asthma attacks per subject per year between treatment groups using a generalized linear model (assuming the Negative Binomial distribution).

The proportion of subjects reporting adverse events (AEs) was summarized for each treatment group using the Medical Dictionary for Regulatory Activities (MedDRA) primary System Organ Class and preferred term.

**Study Population:** Male and female subjects  $\geq 12$  years old with a documented diagnosis of persistent asthma for at least 6 months. Subjects were required to be using a low-to-medium dose of an inhaled corticosteroid (ICS) or a combination of controller medications containing a low (total daily) dose ICS for at least 4 weeks preceding Screening. Subjects had to have a pre-albuterol/salbutamol FEV<sub>1</sub> of  $\geq 50\%$  and  $\leq 85\%$  of predicted normal value at Screening (Visit 1) after withholding asthma medications and demonstrate an increase in FEV<sub>1</sub> of  $\geq 12\%$  over the pre-albuterol/salbutamol FEV<sub>1</sub> within 30 minutes after the inhalation of 2-4 puffs of albuterol/salbutamol. In addition, each subject must have experienced asthma symptoms requiring albuterol/salbutamol use within the 4 weeks preceding Screening. Subjects could not have any current clinically significant condition which would put the safety of the subject at risk through study participation. To be randomized to treatment, subjects had to meet the asthma symptom (score  $\geq 1$  on  $\geq$  any 2 days during the 7 consecutive days immediately prior to the randomization visit) and albuterol use (use on  $\geq$  any 2 days during the 7 consecutive days immediately prior to the randomization visit) criteria while taking FP DISKUS 100 BID during the 14-21 day run-in period.

	FSC DISKUS 250/50	FP DISKUS 250
Number of Subjects:		
Planned, N	289	289
Randomised, N	306	315
Completed, n (%)	225 (74)	242 (77)
Total Number Subjects Withdrawn, N (%)	81 (26)	73 (23)
Withdrawn due to Adverse Events n (%)	10 (3)	3 (<1)
Withdrawn due to Lack of Efficacy n (%)	4 (1)	1 (<1)
Withdrawn for other reasons n (%)	67(22)	69 (22)
<b>Demographics</b>	<b>FSC DISKUS 250/50</b>	<b>FP DISKUS 250</b>
N (ITT)	306	315
Females: Males	191:115	201:114
Mean Age, years (SD)	36.8 (15.52)	39.3 (15.52)
Race, White, n (%)	197 (64)	208 (66)
<b>Primary Efficacy Results:</b>		
<b>Pre-dose FEV<sub>1</sub> (L)</b>	<b>FSC DISKUS 250/50 N=306</b>	<b>FP DISKUS 250 N=315</b>
Mean Baseline (SE)	2.36 (0.042)	2.30 (0.037)
n analyzed	292	309
Mean change from Baseline over Weeks 1-52 (SE)	0.20 (0.017)	0.09 (0.015)
LS mean difference vs. FP DISKUS 250	0.11	
95% CI	0.07, 0.15	

p-value	<0.001	
<b>Secondary Outcome Variables:</b>		
<b>AM PEF (L/min)</b>	<b>FSC DISKUS 250/50 N=306</b>	<b>FP DISKUS 250 N=315</b>
Mean Baseline (SE)	362.3 (6.52)	366.1 (6.47)
n analyzed	299	313
Mean change from Baseline over Weeks 1-52 (SE)	23.6 (2.47)	9.8 (2.40)
LS mean difference vs. FP DISKUS 250	13.4	
95% CI	6.8, 20.0	
<b>Percentage of Symptom-free Days (%)</b>		
Mean Baseline (SE)	20.8 (1.41)	19.7 (1.45)
n analyzed	299	313
Mean change from Baseline over Weeks 1-52 (SE)	37.1 (2.02)	28.5 (1.90)
LS mean difference vs. FP DISKUS 250	9.1	
95% CI	4.1, 14.0	
<b>Asthma Attack Rate</b>		
n analyzed	306	315
Mean (per subject per year)	1.87	2.14
Treatment comparison (FSC/FP) ratio	0.874	
95% CI	0.708, 1.080	
<b>Safety Results:</b>		
<b>Most Frequent Adverse Events – On-Therapy (start of double-blind treatment through end of double-blind treatment)</b>	<b>FSC DISKUS 250/50 N=306 n (%)</b>	<b>FP DISKUS 250 N=315 n (%)</b>
Subjects with any AE(s), n (%)	240 (78)	250 (79)
Upper respiratory tract infection (URTI)	62 (20)	96 (30)
Headache	56 (18)	59 (19)
Nasopharyngitis	54 (18)	56 (18)
Cough	27 (9)	19 (6)
Influenza	22 (7)	25 (8)
Bronchitis	20 (7)	31 (10)
Back pain	20 (7)	14 (4)
Sinusitis	17 (6)	27 (9)
Oropharyngeal pain	14 (5)	20 (6)
Rhinitis allergic	13 (4)	18 (6)
Acute sinusitis	13 (4)	9 (3)
Pyrexia	13 (4)	14 (4)
Viral URTI	12 (4)	10 (3)
Arthralgia	12 (4)	12 (4)
Dyspepsia	12 (4)	4 (1)
<b>Serious Adverse Events - On-Therapy (start of double-blind treatment through end of follow-up period)</b> n (%) [n considered by the investigator to be related to study medication]		

	FSC DISKUS 250/50 N=306 n (%) [related]	FP DISKUS 250 N=315 n (%) [related]
<b>Subjects with non-fatal SAEs, n (%)</b>	14 (5) [0]	10 (3) [0]
Asthma (exacerbation)	3 (<1)	0
Pneumonia	2 (<1)	0
Amoebic dysentery	1 (<1)	0
Cellulitis	0	1 (<1)
Localized infection	0	1 (<1)
Salmonellosis	1 (<1)	0
Pulmonary embolism	1 (<1)	0
Food poisoning	1 (<1)	0
Inguinal hernia, obstructive	0	1 (<1)
Small intestinal obstruction	0	1 (<1)
Myocardial infarction	0	1 (<1)
Myocardial ischemia	0	1 (<1)
Post operative complication	1 (<1)	0
Ulna fracture	1 (<1)	0
Cerebrovascular accident	0	1 (<1)
Acute psychosis	1 (<1)	0
Depression	0	1 (<1)
Deep vein thrombosis	1 (<1)	0
Phlebitis	0	1 (<1)
Iron deficiency anemia	1 (<1)	0
Arthritis	1 (<1)	0
Migraine	1 (<1)	0
Premature baby	0	1 (<1)
<b>Subjects with fatal SAEs, n (%)</b>	0	0

**Conclusion:** FSC DISKUS 250/50 was statistically significantly superior to FP DISKUS 250 at increasing pulmonary function as measured by the change from baseline in pre-dose FEV<sub>1</sub> over a 52-week treatment period. Statistically significant improvements were also observed in AM PEF and the percentage of symptom-free days with FSC DISKUS 250/50 compared with FP DISKUS 250. The mean asthma attack rate was comparable between the treatment groups. The overall incidence of AEs was similar between the treatment groups. The most common AEs were URTI, headache, and nasopharyngitis. SAEs that occurred in more than one subject were asthma exacerbation and pneumonia. No deaths occurred during the study.

**Publications:** None at the time of this report.